IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ALLERGAN SALES, LLC,	§	
	§	
Plaintiff,	§	
	§	
v.	§	CASE NO. 2:12-CV-207-JRG
	§	**(LEAD CASE)**
SANDOZ, INC., et al.	§	
	§	
Defendants.	§	
	§	
	§	
ALLERGAN SALES, LLC,	§	
	§	
Plaintiff,	§	
	§	CASE NO. 2:15-CV-347-JRG
v.	§	
	§	
	§	
SANDOZ, INC., et al.	§	
	§	
Defendants.	§	

FINDINGS OF FACT AND CONCLUSIONS OF LAW

This is a case brought under the Hatch-Waxman Act that concerns Plaintiff Allergan Sales, LLC's ("Allergan") Combigan® (brimonidine tartrate/timolol maleate ophthalmic solution 0.2%/0.5%) eye drops (hereafter "Combigan®") for topical use. Allergan is the holder of approved New Drug Application ("NDA") No. 21-398 for Combigan®. (Dkt. No. 311 at 5.) Additionally, Allergan is the owner by assignment of the patents-in-suit: U.S. Patent Nos. 7,030,149 (the "'149 patent"); 7,320,976 (the "'976 patent"); and 8,748,425 (the "'425 patent"), which are listed in the FDA *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") for Combigan. (*Id.*) Defendant Sandoz, Inc. ("Sandoz") filed its Abbreviated New Drug Application ("ANDA") No. 91-087 with the U.S.

Food & Drug Administration ("FDA"), and Defendants Alcon Laboratories, Inc. and Alcon Research, Ltd. (collectively, "Alcon") filed their ANDA No. 91-574 with the FDA, both of which "seek[] to market generic versions of Allergan's Combigan® product, which Allergan alleges is covered by the patents-in-suit." (*Id.* at 4.)

On April 13, 2012, Allergan sued Sandoz, Alcon, Falcon Pharmaceuticals, Ltd., Apotex Inc., Apotex Corp., and Watson Pharmaceuticals, Inc. (collectively "*Allergan I* Defendants") alleging that the products proposed by the *Allergan I* Defendants' respective ANDAs infringe the asserted claims of the U.S. Patent No. 8,133,890 (the "'890 patent"). (Dkt. No. 1.) On March 9, 2015, Allergan sued Sandoz alleging that the product proposed by Sandoz's ANDA infringes the asserted claims of the patents-in-suit (in addition to certain other patents not presently in suit). (2:15-cv-347, Dkt. No. 1.) These two actions were subsequently consolidated. (Dkt. No. 220.) In October, the parties agreed to dismiss certain claims and counterclaims, leaving the claims between Allergan and Sandoz for infringement and invalidity as to the '149, '976, and '425 patents as the only remaining live claims. (*See* Dkt. No. 334; 2:09-cv-97, Dkt. No. 320.) The Court held a three-day bench trial in this matter from October 25 through October 27, 2016. Presently before the Court are the parties' post-trial proposed findings of fact and conclusions of law. (Dkt. Nos. 347, 348.)

Pursuant to Rule 52 of the Federal Rules of Civil Procedure, the Court issues these Findings of Fact and Conclusions of Law.

FINDINGS OF FACT

I. THE PARTIES

1. Allergan is a limited liability company organized and existing under the laws of the State of Delaware, with a principal place of business at 2525 Dupont Drive, Irvine, California 92612.

2. Sandoz is a Colorado corporation with its principal place of business at 100 College Road West, Princeton, New Jersey 08540.

II. THE ASSERTED PATENTS

3. This is a case filed under the Hatch-Waxman Act after Sandoz sought FDA approval to sell a generic version of Allergan's Combigan® product.

4. The trial in this matter concerned three United States patents: the '149, '976, and '425 patents. The patent claims asserted against Defendants were claim 4 of the '149 patent, claim 1 of the '976 patent, and claims 1–8 of the '425 patent (collectively, the "asserted claims").[1]

5. The named inventors of the patents-in-suit are Chin-Ming Chang, Gary J. Beck, Cynthia C. Pratt, and Amy L. Batoosingh. (*See* PTX-1, PTX-3, PTX-11.)

A. The '149 Patent

6. The '149 patent issued on April 18, 2006, and is titled "Combination of Brimonidine and Timolol for Topical Ophthalmic Use." The application that issued as the '149 patent was filed on April 19, 2002. (PTX-1.) Allergan has asserted Claim 4 of the '149 patent, which covers the improvement in the prior three times a day brimonidine monotherapy "without loss of efficacy" whereby brimonidine is combined with timolol in twice daily dosing. (PTX-1 at 10:10–17.)

7. Claim 4 of the '149 patent is reproduced below:

> A method of reducing the number of daily topical ophthalmic doses of brimondine [*sic*] administered topically to an eye of a person in need thereof for the treatment of glaucoma or ocular hypertension from 3 to 2 times a day without loss of efficacy, wherein the concentration of brimonidine is 0.2% by weight, said

[1] Three other United States Patents, Nos. 7,642,258, 8,133,890, and 8,354,409, were also originally part of this case. Prior to trial in this matter, Allergan, Sandoz, Alcon Laboratories, Inc., Alcon Research, Ltd., and Falcon Pharmaceuticals, Ltd. filed a stipulation of dismissal, dismissing the counts and counterclaims relevant to those patents. (Dkt. 334.)

method comprising administering said 0.2% brimonidine by weight and 0.5% timolol by weight in a single composition.

8. In its Claim Construction Opinion and Order, the Court held that the terms "% by weight" and "% . . . by weight" in claim 4 of the '149 patent mean the "ratio of the weight of the ingredient in question divided by the total volume of the solution, with this ratio expressed as a percentage." (Dkt. No. 241 at 7.) Additionally, the phrase "without loss of efficacy" was construed to mean "without decrease in lowering intraocular pressure." (*Id.* at 28.)

9. The Court further construed "brimonidine" according to its plain and ordinary meaning, "the chemical compound brimonidine, including both its free base and salt forms." (*Id.* at 17.) Similarly, the Court construed "timolol" according to its plain and ordinary meaning, "the chemical compound timolol including both its free base and salt forms." (*Id.* at 20.) Allergan had proposed that "brimonidine" be construed to mean "brimonidine tartrate" and that "timolol" be construed to mean "timolol free base." (*Id.* at 7, 17.) In connection with the constructions of these terms, the Court noted that previously in *Allergan II* "the Court found that Allergan had offered no compelling reason why one chemical compound, brimonidine, should be interpreted as limited to a particular brimonidine salt, while another chemical compound, timolol, should be interpreted as 'timolol free base.' The description of both compounds in the specification and usage in the claims was substantially similar, and the Court could discern no clear reason why the two compounds should be construed in such different manners." (*Id.* at 16.) The Court further stated that "[t]hese reasons are equally applicable here." (*Id.*)

B. The '976 Patent

10. The '976 patent issued on January 22, 2008, and is titled "Combination of Brimonidine and Timolol for Topical Ophthalmic Use." The '976 patent claims priority to U.S. Patent Application No. 10/126,790, which was filed on April 19, 2002. (PTX-3.) The '976

patent has one claim to a method of treating glaucoma or ocular hypertension with a therapeutically effective amount of a fixed combination containing 0.2% brimonidine tartrate and 0.5% timolol administered twice a day. (PTX-3 at 10:13-19.)

11. Claim 1 of the ’976 patent is reproduced below:

> A method of treating glaucoma or ocular hypertension which comprises topically administering a therapeutically effective amount of a single composition comprising brimonidine at a concentration of about 0.2% by weight and timolol at a concentration of about 0.5% by weight in a pharmaceutically acceptable carrier thereof, to the affected eye, wherein said composition is administered twice a day.

12. The Court’s constructions regarding “% by weight,” “brimonidine,” and “timolol,” noted above, also apply to the ’976 patent.

C. The ’425 Patent

13. The ’425 patent issued on June 10, 2014, and is titled “Combination of Brimonidine and Timolol for Topical Ophthalmic Use.” (PTX-11.) The ’425 patent claims priority to U.S. Patent Application No. 10/126,790, which was filed on April 19, 2002. (PTX-11.) The ’425 patent contains eight claims. Claim 1 recites a method of administering a fixed combination containing 0.2% brimonidine tartrate and 0.5% timolol free base administered twice a day, where the method reduces the incidence of certain adverse events compared to administration of three times a day 0.2% brimonidine tartrate monotherapy. (PTX-11 at 9:8–18.) Claims 2–8 each depend from claim 1, and each covers the reduction of a specific adverse event: conjunctival hyperemia (claim 2), oral dryness (claim 3), eye pruritis (claim 4), allergic conjunctivitis (claim 5), foreign body sensation (claim 6), conjunctival folliculosis (claim 7), and somnolence (claim 8). (PTX-11 at 9:19–32.)

14. Claims 1–8 of the ’425 patent are reproduced below:

> 1. A method of treating a patient with glaucoma or ocular hypertension comprising administering twice daily to an affected eye a single composition comprising 0.2% w/v brimonidine tartrate and 0.5% w/v timolol free base,

wherein said method reduces the incidence of one or more adverse events, as compared to the administration of 0.2% w/v brimonidine tartrate monotherapy three times per day wherein the adverse event is selected from the group consisting of conjunctival hyperemia, oral dryness, eye pruritus, allergic conjunctivitis, foreign body sensation, conjunctival folliculosis, and somnolence.

2. The method of claim 1, wherein the adverse event is conjunctival hyperemia.

3. The method of claim 1, wherein the adverse event is oral dryness.

4. The method of claim 1, wherein the adverse event is eye pruritus.

5. The method of claim 1, wherein the adverse event is allergic conjunctivitis.

6. The method of claim 1, wherein the adverse event is foreign body sensation.

7. The method of claim 1, wherein the adverse event is conjunctival folliculosis.

8. The method of claim 1, wherein the adverse event is somnolence.

15. In its Claim Construction Opinion and Order, the Court found that the term "% . . . (w/v)" means the "ratio of the weight of the ingredient in question divided by the total volume of the solution, with this ratio expressed as a percentage." (Dkt. No. 241 at 7.)

16. The Court further construed "brimonidine tartrate" and "timolol free base" according to their plain and ordinary meanings, including both free base and salt forms. (*Id.* at 17, 20.) Also, the phrase "reduces the incidence of" means "reduces the severity and/or rate of occurrence of." (*Id.* at 33.)

D. The Specification of the Patents-In-Suit

17. The '149, '976, and '425 patents share a common specification. The patent specification includes two examples. Example I describes a representative fixed composition of 0.2% brimonidine and 0.5% timolol for use in the asserted method claims. (*See, e.g.*, PTX-1 at 3:38-65.) Example II describes a clinical study comparing the safety and efficacy of a 0.2%

brimonidine/0.5% timolol fixed combination, 0.2% brimonidine monotherapy administered three times per day, and 0.5% timolol monotherapy administered twice per day. (*See, e.g.*, PTX-1 at 4:6-9:8.) Example II includes a clinical study protocol, data comparing the efficacy of the fixed combination to brimonidine monotherapy, and data comparing the incidence of certain adverse events in patients taking the fixed combination to those taking brimonidine monotherapy. (*Id.*)

III. BACKGROUND

18. In 2007, the United States Food and Drug Administration ("FDA") approved Allergan's New Drug Application ("NDA") for Combigan®, a "fixed combination" product for lowering intraocular pressure in glaucoma and ocular hypertension patients. (Dkt. No. 314 at 2.) Allergan has at least six patents that allegedly cover Combigan® and methods of its administration: the '149, '976, '425, and '890 patents, in addition to U.S. Patent Nos. 7,642,258 (the "'258 patent") and 8,354,409 (the "'409 patent"). (*Id.*) These patents are listed in the FDA's "Orange Book." (*Id.*)

A. History of the Litigation and Procedural Posture

1. *Allergan I*

19. On or about February 23, 2009, Allergan received a Paragraph IV letter from Sandoz regarding the '149 and '976 patents. (C.A. No. 2:09-cv-097, Dkt. No. 1 at ¶ 15.) The letter indicated that Sandoz had submitted ANDA No. 91-087 for the purpose of obtaining approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan® prior to the expiration of the '149 and '976 patents. (*Id.*)

20. On April 7, 2009, Allergan filed a Complaint for infringement of the '149 and '976 patents against Sandoz, alleging that the filing of ANDA No. 91-087 constituted an act of infringement of the '149 and '976 patents. (C.A. No. 2:09-cv-097, Dkt. No. 1.) ("*Allergan I*"). On November 9, 2009, Allergan filed an Amended Complaint to add allegations of infringement

of U.S. Patent No. 7,323,463 ("the '463 patent"). (C.A. No. 2:09-cv-097, Dkt. No. 37.) On March 19, 2010, Allergan filed a Second Amended Complaint against Sandoz to additionally assert the '258 patent. (C.A. No. 2:09-cv-097, Dkt. No. 80.)

21. On or about September 29, 2009, Allergan received a Paragraph IV letter from Alcon regarding the '149, '976, and '463 patents. The letter indicated that Alcon had submitted ANDA No. 91-574 for the purpose of obtaining approval to commercially manufacture, use, offer for sale, or sell a generic version of Combigan® prior to the expiration of the '149, '976, and '463 patents.

22. On November 6, 2009, Allergan filed a Complaint for infringement of the '149, '976, and '463 patents against Alcon, alleging that the filing of ANDA No. 91-574 constituted an act of infringement of the '149, '976, and '463 patents. (C.A. No. 2:09-cv-348, Dkt. No. 1.) On April 28, 2010, Allergan filed an Amended Complaint against Alcon to additionally assert the '258 patent.

23. C.A. No. 2:09-cv-097 and C.A. No. 2:09-cv-348 were consolidated, along with other Hatch-Waxman actions Allergan had filed against other generic pharmaceutical companies relating to Combigan®, for pretrial and trial purposes.

24. The Court granted Sandoz's motion for summary judgment of non-infringement of claims 1–3 of the '149 patent, finding that Sandoz's proposed product was not covered by those claims. *Allergan, Inc. v. Sandoz Inc.*, 818 F. Supp. 2d 974, 982 (E.D. Tex. 2011).

25. Sandoz did not dispute that its proposed ANDA product infringed claim 4 of the '149 patent and claim 1 of the '976 patent. On August 2, 2011, Sandoz entered into a stipulation that its proposed product described in ANDA No. 91-087 meets all of the limitations of claim 4 of the '149 patent and claim 1 of the '976 patent. (C.A. No. 2:09-cv-097, Dkt. No. 234.)

26. The Court held a four-day bench trial on the validity of the ’149, ’976, ’258, and ’463 patents on August 2, 2011 through August 5, 2011. The Court subsequently found that the *Allergan I* Defendants infringed, among other claims, claim 4 of the ’149 patent and claim 1 of the ’976 patent, that the asserted claims were not invalid, and enjoined the *Allergan I* Defendants from selling their generic products. (C.A. No. 2:09-cv-097, Dkt. No. 262.)

27. The *Allergan I* Defendants appealed the Court’s decision of no invalidity in the *Allergan I* case to the United States Court of Appeals for the Federal Circuit.

28. On May 1, 2013, the Federal Circuit issued its opinion in the *Allergan I* case. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286 (Fed. Cir. 2013) (PTX-246). The Federal Circuit held that claim 4 of the ’149 patent was not invalid as obvious. *Id.* at 1294. In making that determination, the Federal Circuit noted that the “record firmly establishes that when brimonidine is dosed twice per day as opposed to three times per day, there is a loss of efficacy in the afternoon—the so called, afternoon trough.” *Id.* The Federal Circuit concluded that the *Allergan I* Defendants “failed to point to evidence in the prior art that would allow us to conclude that the addition of timolol to brimonidine dosed twice per day would eliminate the afternoon trough issue.” *Id*. The prior art relied on by the *Allergan I* Defendants before the Federal Circuit included the DeSantis (DTX-1051), Timmermans (DTX-1150), Larsson (DTX-1121), Clineschmidt (DTX-1169), and Airaksinen (DTX-1331) references—the same references Sandoz relies on for its obviousness arguments here. *Id.* at 1289–90.

29. The Federal Circuit further considered serial administration, also referred to as adjunctive or concomitant administration, of brimonidine and timolol dosed twice per day as prior art to claim 4 of the ’149 patent. The Federal Circuit held that “while it is true that the prior art shows concomitant administration of brimonidine and timolol was dosed twice per day, this

art does not show that there was no loss of efficacy associated with that treatment, let alone an elimination of the afternoon trough" and found that claim 4 was not invalid over this art. *Id.* at 1294.

30. The Federal Circuit in the *Allergan I* case also considered unexpected results, in particular the district court's finding that there was increased efficacy and reduction in side effects from the administration of Combigan® compared to brimonidine administered three times per day. *Id.* at 1293. The Federal Circuit accepted the district court's factual findings regarding the existence of these secondary factors. *Id*. Further, the Federal Circuit agreed that it was unexpected that Combigan® dosed twice per day did not show a loss of efficacy as compared to brimonidine 0.2% administered three times per day. *Id*. The Federal Circuit did not find these unexpected results to be meaningful its analysis of the formulation claims of the '463 patent, which covered only a fixed combination of 0.2% brimonidine and 0.5% timolol in a single composition. *Id*. As a result, the Federal Circuit found that the claims of the '463 patent were obvious. *Id*. However, the Federal Circuit also held that "the unexpected benefits of twice a day dosing of the combination formula are relevant to Sandoz's attack on the validity of the method claims," and based in part on those unexpected results, found that claim 4 of the '149 patent was not obvious. *Id*. at 1293–94.

31. Because the '149, '976, and '258 patents expire on the same day, April 19, 2022, the Federal Circuit found it unnecessary to address the claims of the '976 and '258 patents after concluding that claim 4 of the '149 patent was not invalid. *Id.* at 1294 n.2.

32. The *Allergan I* Defendants subsequently petitioned the Federal Circuit for rehearing *en banc*, and filed a writ of certiorari with the U.S. Supreme Court, which were both denied. *Sandoz Inc. v. Allergan, Inc.*, 134 S. Ct. 1764 (2014).

2. Sandoz's Subsequent Attempts to Challenge the Validity of the Patents-In-Suit

33. While the appeal in *Allergan I* was pending, the *Allergan I* Defendants moved to modify the Court's injunction order under Fed. R. Civ. P. 60(b), arguing that they had modified their ANDA, and that their proposed product would no longer infringe claim 4 of the '149 patent. (C.A. No. 2:09-cv-097, Dkt. No. 280.) The Court denied the *Allergan I* Defendants' motion, and the Federal Circuit affirmed that denial without opinion. (C.A. No. 2:09-cv-097, Dkt. No. 308; C.A. No. 2:09-cv-097, Dkt. No. 316.)

34. Sandoz's entire amendment to its ANDA No. 91-087[2] is the deletion of two words, "glaucoma or" throughout its proposed package insert. An example of that change to Sandoz's proposed package insert is as follows, from the indications and usage section:

---------- **INDICATIONS AND USAGE** ----------

Brimonidine tartrate and timolol maleate ophthalmic solution is an alpha adrenergic receptor agonist with a beta adrenergic receptor inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with ~~glaucoma or~~ ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP; the IOP-lowering of brimonidine tartrate and timolol maleate ophthalmic solution dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution, 0.5% dosed twice a day and brimonidine tartrate ophthalmic solution, 0.2% dosed three times per day. (1)

(PTX-016A at SDZ(33)0003360.) Sandoz also made that same change to other portions of its package insert, including the clinical data section. (*See* PTX-016A at SDZ(33)0003371.) Despite removing "glaucoma" from its package insert, Sandoz confirmed that the clinical data listed on their label as to both efficacy and side effects is the same as on the Combigan® label,

[2] In approximately 2011, Sandoz and Alcon merged their separate ANDAs into ANDA No. 91-087. (Trial Tr., Day 1 PM at 122:5-8 (Herrick); Dkt. 311 at 17.)

and was taken from clinical trials on patients with both glaucoma and ocular hypertension. (Trial Tr., Day 2 AM at 47:21-50:13 (Tanna).)

35. Sandoz's witnesses and its counsel confirmed that the composition and chemistry of its proposed ANDA product is identical to the product litigated in *Allergan I*. (*See, e.g.*, Trial Tr., Day 2 AM at 39:8-11 (Tanna); Dkt. 293, Ex. 2 at 28:1-8, 30:22-31:9.)

3. *Allergan II*

36. In March 2012, while *Allergan I* was still pending in this Court, the '890 patent issued. (Dkt. No. 1 ¶ 23.) Allergan filed an additional action alleging that Sandoz's ANDA and proposed product described therein infringed the '890 patent ("*Allergan II*"). (Dkt. No. 1.) On March 15, 2013, Sandoz amended its pleadings to add counterclaims for non-infringement and invalidity of the '409 patent, which had later issued, to those for non-infringement and invalidity of the '890 patent. (Dkt. No. 314 at 4.)

37. The *Allergan II* case was set for trial in January 2014, but trial in that matter was stayed in December 2013 pending the appeal of Sandoz's Rule 60 motion in the *Allergan I* case. (Dkt. No. 311 at 7.)

4. *Allergan III*

38. On or about January 23, 2015, Allergan received a Paragraph IV letter from Sandoz regarding the '149, '976, '258 and '425 patents. On March 9, 2015, Allergan filed a Complaint for infringement of the '149, '976, '258 and '425 patents against Sandoz, alleging that the proposed generic product described in ANDA No. 91-087, as amended, infringed those patents. (C.A. No. 2:15-cv-347, Dkt. No. 1.) That action was consolidated with *Allergan II*. (Dkt. 220.) The '890, '409, and '258 patents were subsequently dismissed by stipulation prior to trial. (Dkt. Nos. 311, 334.)

39. The Court held a bench trial from October 25, 2016 through October 27, 2016 on infringement and validity of claim 4 of the ’149 patent, claim 1 of the ’976 patent, and claims 1–8 of the ’425 patent.

B. Background of the Technology

1. Elevated Intraocular Pressure

40. Intraocular pressure (“IOP”), the pressure inside the eye, is what allows the eyeball to keep its shape. (Trial Tr., Day 1 PM at 27:4–28:7 (Noecker).) In a normal eye, intraocular pressure is between approximately 10 and 22 millimeters of mercury (mmHg). (*Id.*) However, when intraocular pressure becomes too high, that elevated intraocular pressure can potentially cause damage to the optic nerve, leading to the death of nerve cells and corresponding vision loss. (Trial Tr., Day 1 PM at 28:18–29:25 (Noecker), Trial Tr., Day 1 PM at 147:19–24 (Tanna).) When a patient has elevated intraocular pressure without detectable damage to the optic nerve, they are generally diagnosed as having ocular hypertension. (Trial Tr., Day 1 PM at 30:13–31:2 (Noecker); *see also* Trial Tr., Day 2 PM at 147:9-–48:8 (Tanna).) Once damage to the optic nerve is detected, the patient is typically diagnosed as having glaucoma. (Trial Tr., Day 1 PM at 28:18–29:25 (Noecker), Trial Tr., Day 1 PM at 147:9–148:4 (Tanna).)

41. Determining whether a patient has ocular hypertension or glaucoma is often difficult, as it can be challenging to determine when the optic nerve has suffered damage. (Trial Tr., Day 1 PM at 30:13–31:2 (Noecker).) Clinicians may suspect that a patient is suffering from damage to the optic nerve, yet be unable to know it with certainty. (*Id.*; Trial Tr., Day 1 PM at 149:18–150:3 (Tanna).)

42. While ocular hypertension is a major risk factor for glaucoma development, the majority of patients with ocular hypertension never develop the damage to the optic nerve that defines glaucoma. (Trial Tr., Day 1 PM at 148:6–22 (Tanna).) For this reason, patients with

ocular hypertension and those with glaucoma comprise different patient populations. (Trial Tr., Day 1 PM at 31:3–10 (Noecker).) However, while the treatment of patients with ocular hypertension may differ from the treatment of those with glaucoma, the first line therapy for both ocular hypertension and glaucoma is to reduce eye pressure through administration of eye drops. (Trial Tr., Day 1 PM at 31:3–10, 32:18–33:7 (Noecker).) Patients with greater intraocular pressure, however, may require laser or surgical procedures. (Trial Tr., Day 1 PM at 33:2-7 (Noecker).)

43. The United States Food & Drug Administration ("FDA") treats glaucoma and ocular hypertension in the same way with respect to approval of drugs to treat those disease states. (Trial Tr., Day 1 AM at 38:8–39:4 (Batoosingh) (stating that FDA requires data to be separated by "key demographic subpopulations," such as age, race, sex, and iris color, but has not ever asked for separate analysis of glaucoma and ocular hypertension patients).) All glaucoma and ocular hypertension drugs are approved to lower IOP. (Trial Tr., Day 2 PM at 35:7–9 (Samples).) As all of the clinical experts in this case agreed, there are no IOP-lowering drugs approved only for the treatment of glaucoma and not ocular hypertension. (Trial Tr., Day 2 PM at 35:10–17 (Samples); Day 2 AM at 30:5-14 (Tanna); Day 1 PM at 34:16–23 (Noecker).) There are also no IOP-lowering drugs approved only for the treatment of ocular hypertension and not glaucoma. (*Id*.)

2. Fixed Combination Drugs Generally

44. A fixed combination formulation is a combination of two different drugs in a single formulation within a single bottle. (Trial Tr., Day 1 AM at 39:22–40:1 (Batoosingh).)

45. Historically, the FDA has approved very few fixed combination drugs. As of 2001, before the filing of the patents related to Combigan®, there was only one marketed, FDA-approved fixed combination—Cosopt®. (Trial Tr., Day 2 PM at 126:7–11 (Noecker); Trial Tr.,

Day 1 AM at 46:10–19 (Batoosingh).) Moreover, the FDA has repeatedly expressed skepticism about fixed combination products and has set a high bar for approval. *See, e.g.*, 21 C.F.R. § 300.50 (setting forth requirements for approval of fixed combination drugs). Even today, there are only three fixed combination glaucoma products currently approved and sold for glaucoma treatment in the United States—Cosopt®, Simbrinza®, and the product at issue in this litigation, Combigan®. (Trial Tr., Day 1 PM at 34:4-–5 (Noecker).)

46. Prior to the development of Combigan®, Allergan had also experienced failures in developing fixed combination drugs. In particular, Allergan had attempted to develop two separate fixed combinations using its beta-blocker, levobunolol (which is sold under the trade name Betagan®), with two other glaucoma medications, pilocarpine and Propine. (Trial Tr., Day 1 AM at 41:13–23 (Batoosingh).) As Ms. Batoosingh explained, development of the Betagan® and pilocarpine fixed combination was halted after the clinical development group had estimated that there was only a 30% probability that the combination would be more efficacious than either agent alone. (PTX-194-0003 ("Clinical research determined a 30% probability of success to show clinically that the combination more efficacious than either component alone."); Trial Tr., Day 1 AM at 44:7-19 (Batoosingh) ("[T]he chance of being able to see that one plus one equals two was very, very low and that one plus one may not even equal one. Had about a 30 percent probability that we would be able to do better than that.").)

47. With respect to the Betagan® and Propine combination, Allergan was never able to get it FDA approved and on the market in the United States. (Trial Tr., Day 1 AM at 45:20–25 (Batoosingh) (explaining that Betagan®/Propine did not get approved "[b]ecause the benefit of putting the two drugs in the – in the same bottle did not outweigh the risk").) As is evidenced by the fact that only three fixed combination products have been FDA approved in the past 20

years, Allergan's competitors also had similar challenges. (Trial Tr., Day 1 AM at 45:2–4 (Batoosingh).)

3. The Development of Alphagan® and Timoptic®

48. The patents-in-suit are directed to the fixed combination of two active ingredients: (1) brimonidine, and (2) timolol, for the targeted lowering of IOP in patients with glaucoma or ocular hypertension. (Trial Tr., Day 1 PM 40:21–41:9 (Noecker).) Prior to their combination in Combigan®, however, both brimonidine and timolol had been marketed separately as Alphagan® and Timoptic®, respectively.

a. Alphagan®

49. Brimonidine tartrate 0.2%, which was marketed by Allergan as Alphagan®, was developed by Allergan as a new glaucoma medication in the late 1980s and early 1990s. (Trial Tr., Day 1 AM at 50:23-51:5, 54:15-55:20 (Batoosingh).) Brimonidine is an $alpha_2$ adrenergic agonist that lowers IOP in glaucoma patients by reducing fluid production in the eye while also increasing outflow of that fluid from the eye. (Trial Tr., Day 1 AM at 50:15-20 (Batoosingh).) The FDA approved Alphagan® in 1996. (Trial Tr., Day 1 AM at 50:23-51:5 (Batoosingh); Trial Tr., Day 1 PM at 152:1-3 (Tanna).)

50. Unlike many glaucoma medications, which are dosed twice daily (once in the morning and once in the evening, i.e., "BID"), the FDA only approved Alphagan® for dosing three times daily (i.e., "TID") due to lower efficacy of the drug with less frequent dosing. (Trial Tr., Day 1 AM at 51:8–24, 54:19–55:5, 56:2–15 (Batoosingh).) As explained further below, twice-daily dosing with Alphagan® 0.2% results in an approximately 3.25 mmHg higher IOP in the afternoon than three times daily. (Trial Tr., Day 1 AM at 51:8–24 (Batoosingh); PTX-291-0122.) Brimonidine's loss of efficacy in the afternoon, about 7–9 hours post-dosing, was referred to at trial as the "afternoon trough." (Trial Tr., Day 1 AM at 67:16–68:9 (Batoosingh).)

Allergan attempted to secure FDA approval for Alphagan® as a twice-daily drug but was unable to do so. (Trial Tr., Day 1 AM at 51:8–13 (Batoosingh); Trial Tr., Day 2 PM at 128:15–17 (Noecker).)

51. Certain adverse side-effects limited the utility of Alphagan®. (Trial Tr., Day 1 AM at 57:21–23, 58:19–59:2 (Batoosingh); Trial Tr., Day 2 PM at 137:5-19 (Noecker); PTX-147-0009.) Specifically, brimonidine 0.2% was found to cause a high rate of ocular allergy, which led many patients to discontinue using the drug. (Trial Tr., Day 1 AM at 58:19-59:3 (Batoosingh); Trial Tr., Day 2 PM at 137:5–19 (Noecker).) Once a patient develops an allergy to brimonidine, brimonidine is no longer available as a treatment option for that patient. (Trial Tr., Day 2 PM at 138:12–19 (Noecker).) Additionally, brimonidine was also known to cause systemic side effects, including somnolence and dry mouth. (Trial Tr., Day 1 PM at 58:24–59:15 (Noecker); Trial Tr., Day 2 AM at 129:6-130:7; 131:14-18 (Samples); PTX-13A at AGN_COMBI0007632; PTX-034-0012; PTX-070-0007.) The high incidence of these various side effects in patients treated with brimonidine monotherapy is reported throughout the literature. (*See, e.g.* PTX-034-0012; PTX-070-0005-7.)

b. Timoptic®

52. Timolol, a beta-blocker, was developed by Merck in the 1970s. The FDA first approved it as a treatment for glaucoma in 1978, and it was sold under the brand name Timoptic®. (Trial Tr., Day 1 AM at 47:3–20 (Batoosingh).) Timoptic® is identified in its label as containing 0.5% timolol (6.8 mg/mL of timolol maleate). (PTX 146-0001.) Timoptic® is typically prescribed either once or twice daily. (Trial Tr., Day 1 AM at 48:18-21 (Batoosingh); PTX-146-0006.) Timoptic® lowers IOP by suppressing aqueous humor production. (Trial Tr., Day 1 AM at 47:7-11 (Batoosingh).) Since its approval in 1978, Timoptic® has been the "gold

standard" to which the FDA compares all other new glaucoma medications. (Trial Tr., Day 1 PM at 151:19–21 (Tanna).)

c. Concomitant Administration of Alphagan® and Timoptic®

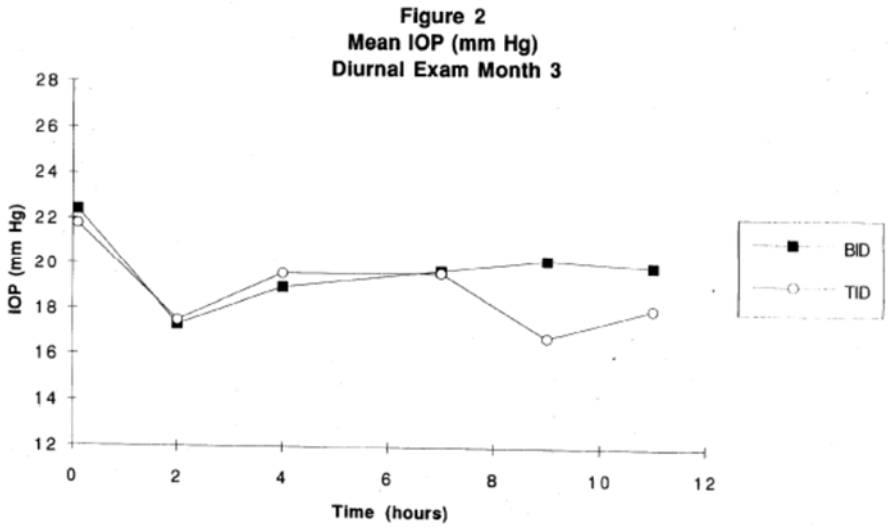
53. Both Dr. Tanna and Dr. Noecker testified that prior to the development and approval of Combigan® they would prescribe brimonidine and timolol dosed two times per day concomitantly to patients. (Trial Tr., Day 1 PM at 154:7–16 (Tanna); Trial Tr., Day 3 AM 21:12-22:2 (Noecker).) Indeed, the '149 patent states in the "Background of the Invention" that combinations of brimonidine and timolol were available for separate use in the ophthalmic art and were combined in serial application to treat glaucoma. (PTX11 at 1:7–12.) Further, the Federal Circuit has recognized that "[a]t the time of the invention, it was known that the serial administration of brimonidine and timolol reduced intraocular pressure greater than either timolol or brimonidine alone. Moreover, [prior art] expressly provided a motivation to formulate fixed combinations of alpha$_2$-agonists [such as brimonidine] and beta blockers, including timolol, in order to increase patient compliance." *Allergan*, 726 F.3d at 1291.

54. Concomitant dosing requires a waiting period of about two to five minutes between the doses, and oftentimes people forget to use the second medication; thus, such treatment regimens often suffer from patient compliance issues. (Trial Tr., Day 1 PM at 156:2–14 (Tanna).) Concomitant and serial are both terms referring to administering two different drugs in separate bottles to a single patient. (Trial Tr., Day 1 PM at 155:13–23 (Tanna).)

4. Brimonidine Exhibits Reduced Efficacy When Dosed Twice Per Day

55. As Ms. Batoosingh, the clinical lead for Allergan and an inventor on the patents-in-suit explained at trial, reducing the dose frequency of brimonidine to twice per day from three times per day would be expected to result in reduced IOP-lowering efficacy. (Trial Tr., Day 1 AM at 67:16–69:3 (Batoosingh); *id.* at 71:7–18)

56. The reason for that expectation was that those of skill in the art, including Ms. Batoosingh and others at Allergan, knew that there was a significant difference in the IOP-lowering effect of brimonidine dosed twice daily compared to brimonidine dosed three times daily. (Trial Tr., Day 1 AM at 54:19–55:2 (Batoosingh); PTX-291-0122.) In support of its NDA for Alphagan®, Allergan submitted, among other things, clinical study A342-119-7831, which compared the IOP lowering effect of twice-daily dosed brimonidine with three times daily dosed brimonidine. (PTX-291.) That study showed that at hour nine, two hours after the three times daily ("TID" in the graph below) group received their second dose of brimonidine and nine hours after the first (and only) dose of brimonidine was administered to the twice daily ("BID" in the graph below) group, there was approximately a 3.25 mmHg difference in IOP lowering effect between the two groups:



(PTX-291-0122; *see also* PTX-291-0062-63 (showing that the mean change in IOP was -2.07 for the twice daily group and -5.31 for the three times daily group at hour 9, a difference that was statistically significant with a p value of <0.001).) That 3.25 mmHg difference between the

twice daily and three times daily groups was both statistically significant, and was a significant difference from a patient health perspective. (Trial Tr., Day 1 AM at 54:19–55:2 (Batoosingh).)

57. The inventors did not believe that the addition of timolol in the Combigan® formulation would make up the more than 3 mmHg loss of efficacy that was the result of reducing the dosing of brimonidine from three to two times per day:

> Q. And was that result expected by you and your team when you began the clinical trial?
> A. No, it was not.
> Q. And why not?
> A. Because we didn't expect timolol's efficacy could be able to demonstrate an additional 3-1/4 millimeter of IOP-lowering on top of Alphagan to be able to close that gap.

(Trial Tr., Day 1 AM at 78:6–12 (Batoosingh).)

58. Moreover, the prior art showed that timolol did not add enough IOP-lowering efficacy to make up for the more than 3 mmHg loss of efficacy caused by reducing the dosing frequency of brimonidine. (Trial Tr., Day 1 AM at 69:5–13 (Batoosingh) ("Now, did the prospect of combining brimonidine and timolol – we heard in opening that that, of course, everybody knew that would fill that efficacy gap. Did you – did you believe that combining it with timolol would fill that efficacy gap? A. No. The Phase 3 trials that we conducted with Alphagan showed that the peak effect of both drugs was the same. So there was no belief that we would be able to increase the effect versus Alphagan just by having timolol on board.").)

59. Instead, the Larsson reference, one of the pieces of prior art relied on by Sandoz here, showed that when added to brimonidine, timolol added only 1.7 mmHg of additional IOP lowering in the afternoon. (DTX-1121 at 494, Table 2; Trial Tr., Day 2 AM at 59:1–60:10 (Tanna).) Additionally, Clineschmidt, another prior art reference relied on by Sandoz, which relates to the fixed combination of dorzolamide and timolol (marketed as Cosopt®), showed that

in the morning, at the peak effect of timolol, the addition of timolol added only 1.2 to 2.4 mmHg of IOP lowering to dorzolamide alone. (DTX-1169 at DEFS(B/T)000030; Trial Tr., Day 2 PM at 168:3–169:2 (Noecker) (noting that even in the "best case scenario," where timolol was at its peak effect, it added only 1.2 to 2.4 mmHg of IOP lowering).)

60. Defendants presented no evidence to show that timolol could be expected to make up the more than 3 mmHg loss of IOP lowering at hour 9. Additionally, the Federal Circuit previously found that "while it is true that the prior art shows concomitant administration of brimonidine and timolol was dosed twice per day, this art does not show that there was no loss of efficacy associated with that treatment, let alone an elimination of the afternoon trough." *Allergan*, 726 F.3d at 1294. For these reasons, the Court finds that a person of skill in the art would have expected that a fixed combination of 0.2% brimonidine and 0.5% timolol dosed twice per day would have exhibited less IOP-lowering efficacy at than 0.2% brimonidine dosed three times per day, especially at the late afternoon time point.

5. Combining Brimonidine and Timolol Was Not Expected to Succeed

61. As detailed above, brimonidine has significant and problematic side effects. As shown on the label for Alphagan®, the original 0.2% brimonidine product released by Allergan in 1996, the rates of oral dryness, ocular hyperemia, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus were 10-30%. (PTX-147A-0009.)

62. Similarly, timolol also has a significant side effect profile, and exhibits many of the same adverse events as does brimonidine. The label for timolol shows that many of the same adverse events that were problematic for brimonidine were also seen with timolol, including asthenia/fatigue, dry mouth, somnolence, foreign body sensation, and itching, among other things. (PTX-146-0005.) Due to its side effects, treatment with timolol is contraindicated in a

number of patients. (Trial Tr., Day 1 PM at 150:7–151:10 (Tanna).) For example, the label of the Alphagan® products contains the following warning about using brimonidine with a beta-blocker like timolol:

> Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

(PTX-147A-0008.)

63. When two active ingredients like brimonidine and timolol are combined into a single bottle, the expectation is that the adverse events of each of those active ingredients would be exacerbated, not reduced. (Trial Tr., Day 2 PM at 145:2–12 (Noecker).) By adding two drugs into one bottle for twice-daily dosing, Dr. Noecker explained that the result is "four medications," specifically "two [doses] of timolol and two [doses] of brimonidine." (Trial Tr., Day 2 PM at 145:15-146:2 (Noecker); Trial Tr., Day 2 AM at 84:7–85:20 (Schiffman) (explaining that, when two drugs are combined together "you may experience a worse event profile from having done that. I think you may expect a generally similar adverse event profile; that putting them together would actually, in a very significant way, alleviate the adverse events of one or the other, practically shocking.").)

64. Similarly, Ms. Batoosingh explained that the inventors expected the adverse events to increase if two drugs were combined in one bottle, specifically discussing the adverse events listed on the Timoptic® label:

> Q. All right. Now, looking at these, were there any of them that you regarded as particularly significant in your work on the Combigan® project?
> A. All of them.
> Q. Why?
> A. Because you're taking two drugs and putting them into the same bottle, so you expect to get the side effects from each. And if there are side effects that the two drugs share, you may actually exacerbate the side effects.

(Trial Tr., Day 1 AM at 49:13–21 (Batoosingh).) Ms. Batoosingh pointed out the side effects that brimonidine and timolol share, and she referenced foreign body sensation as an example of one side effect that she would expect to be exacerbated by combining the two drugs. (Trial Tr., Day 1 AM at 49:22–50:12 (Batoosingh).)

65. The literature on other fixed combination products also reflected an expectation of exacerbation of side effects, which would have led a person of skill in the art to believe that combining brimonidine and timolol would similarly increase adverse effects. In particular, the adverse event data on Cosopt® shows that when dorzolamide and timolol were combined, the adverse events were the same as or worse than the individual components. (Trial Tr., Day 2 PM at 151:17–155:8 (Noecker).) The exacerbation of side effects in Cosopt® was studied by Dr. Boyle. In Dr. Boyle's study, patients received either three-times per day dorzolamide; twice per day timolol; or twice per day Cosopt®, which is a fixed combination of dorzolamide and timolol. (PTX-393-0001; Trial Tr., Day 2 PM at 152:11–18 (Noecker).) Boyle found that many of the adverse events were experienced more frequently in the patients receiving the fixed combination twice per day than in the patients receiving dorzolamide three times per day, even though the patients on Cosopt® were getting one less dose of dorzolamide. (PTX-393-0006.)

66. Moreover, simply reducing the dosage of 0.2% brimonidine from three times daily to twice daily would not have led to a reduction in adverse events. Allergan's data, and all of the data in the prior art, demonstrates that there is no difference in the side effect profile between 0.2% brimonidine dosed three times per day and 0.2% brimonidine dosed twice per day. (DTX-1110 at S24-S25; Trial Tr., Day 2 PM at 17:24–18:8 (Samples) ("Q. And you wouldn't rely on this difference of one patient to draw any conclusions about the relative rates of adverse events among twice-daily and three-times-a-day dose of brimonidine, correct? A. The

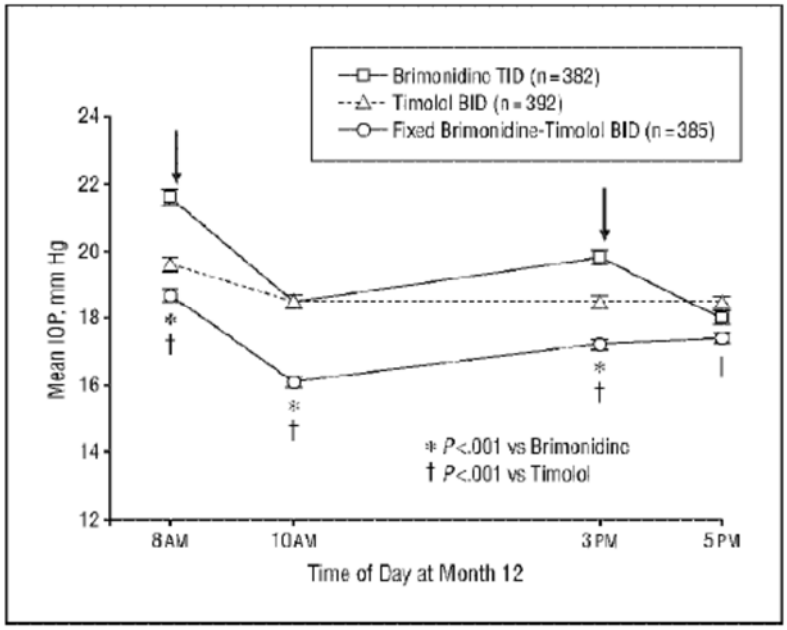
difference [shown in Walters] is small, so I would not."); PTX-034-0012 ("the profile and incidence of ocular and systemic adverse events are similar with twice-daily and 3-times-daily administration"); Trial Tr., Day 2 PM at 150:2-151:8 (Noecker).)

67. For these reasons, the Court finds that a person of ordinary skill in the art would have expected that by combining two drugs in one bottle the associated adverse events would be exacerbated not reduced. (Trial Tr., Day 2 PM at 155:5–8 (Noecker).)

6. Development of Combigan®

a. Combigan® Reduced the Amount of Brimonidine Doses from Three to Two Without Loss of Efficacy

68. Despite its initial expectations, Allergan was able to demonstrate that the dosing for brimonidine could be reduced from the three-times-a-day required for Alphagan® to a more convenient two-times-a-day dosing for Combigan® while maintaining equal efficacy to the three times a day dosing. (Trial Tr., Day 1 AM at 76:25–78:12 (Batoosingh).) Specifically, Allergan was able to eliminate the afternoon trough in IOP lowering that had previously been shown to occur when brimonidine was dosed only twice a day. (*See, e.g.*, PTX-70.) In the two pivotal clinical trials on Combigan®, numbered 190342-012T and 190342-013T (the "012T study" and "013T study," respectively) Allergan was able to show that Combigan® dosed twice daily ("Fixed Brimonidine-Timolol BID" in the graph below) showed numerically better and statistically equivalent IOP lowering compared to brimonidine monotherapy dosed three times daily ("Brimonidine TID" in the graph below):



(PTX-70-0006.) As Ms. Batoosingh testified,

> Q. All right. What does this graph show about the results for the efficacy of Combigan versus brimonidine three times a day and timolol twice a day?
> A. It shows that Combigan lowered intraocular pressure better than either of the components through 3:00 p.m., better than timolol at 5:00 p.m. and the same as brimonidine at 5:00 p.m.

(Trial Tr., Day 1 AM at 76:25–77:5 (Batoosingh).)

69. The fact that Combigan® was able to eliminate the significant difference that had previously been observed and reported for twice a day brimonidine versus three times a day brimonidine was surprising to the inventors, to Allergan, and to the industry. As Ms. Batoosingh testified:

> Q. And was that result expected by you and your team when you began the clinical trial?
> A. No, it was not.
> Q. Any why not?
> A. Because we didn't expect timolol's efficacy could be able to demonstrate an additional 3-1/4 millimeter of IOP-lowering on top of Alphagan to be able to close that gap.

(Trial Tr., Day 1 AM at 78:6–12 (Batoosingh).)

70. Similarly, Allergan's expert, Dr. Noecker testified that one of skill in the art would have found the efficacy effect shown with Combigan® to be surprising and unexpected. (Trial Tr., Day 2 PM at 132:9–23 (Noecker).)

b. Combigan® Reduced the Incidence of Certain Adverse Events Compared to Brimonidine Three Times Daily

71. In addition to Combigan®'s surprising efficacy results, the same pivotal clinical trials demonstrated that combining brimonidine and timolol for twice-daily dosing resulted in an unexpected reduction in certain adverse events as compared to brimonidine alone dosed three times daily. The pooled data from the 12T and 13T studies reflects that Combigan® showed a statistically significant reduction in a number of different adverse events, including each of the claimed adverse events, as compared to brimonidine alone:

	Combigan® BID	Brimonidine 0.2% TID	Timolol 0.5% BID
Oral Dryness	8 (2.1%)	36 (9.4%)	2 (0.5%)
Somnolence	6 (1.6%)	15 (3.9%)	2 (0.5%)
Conjunctival Hyperemia	66 (17.1%)	90 (23.6%)	31 (7.9%)
Eye Pruritus	22 (5.7%)	47 (12.3%)	15 (3.8%)
Allergic Conjunctivitis	20 (5.2%)	37 (9.7%)	2 (0.5%)
Conjunctival Folliculosis	19 (4.9%)	35 (9.2%)	7 (1.8%)
Foreign Body Sensation	8 (2.1%)	19 (5.0%)	7 (1.8%)

(PTX-13F at AGN_COMBI0006288-90; *see also* at AGN_COMBI0006283-84.)

72. As an example, the 012T and 013T studies demonstrated a statistically significant reduction in the incidence of conjunctival hyperemia, eye pruritus, allergic conjunctivitis, conjunctival folliculosis, and oral dryness in patients receiving Combigan® compared to patients receiving brimonidine three times daily:

Table 2. Treatment-Related Adverse Events by Treatment Group*

Adverse Event	Fixed Brimonidine-Timolol BID Group (n = 385)	Brimonidine TID Group (n = 382)	*P* Value (Combination vs Brimonidine)†	Timolol BID Group (n = 392)	*P* Value (Combination vs Timolol)†
Overall	204 (53.0)	240 (62.8)	.006	160 (40.8)	<.001
Conjunctival hyperemia	56 (14.5)	87 (22.8)	.003	29 (7.4)	.001
Ocular stinging	24 (6.2)	11 (2.9)	.03	26 (6.6)	.82
Eye pruritus	21 (5.5)	42 (11.0)	.005	11 (2.8)	.06
Allergic conjunctivitis	20 (5.2)	36 (9.4)	.02	1 (0.3)	<.001
Conjunctival follicuiosis	19 (4.9)	35 (9.2)	.02	7 (1.8)	.02
Oral dryness	8 (2.1)	35 (9.2)	<.001	2 (0.5)	.06
Conjunctival allergy/inflammation‡	100 (26.0)	152 (39.8)	<.001	47 (12.0)	<.001

(PTX-070-0007; *see also* Trial Tr., Day 1 AM at 78:20–81:2 (Batoosingh).)

73. The reduction in allergic conjunctivitis, commonly called ocular allergy, was particularly significant, because a high incidence of this adverse event had been long associated with brimonidine 0.2%. (Trial Tr., Day 2 PM at 137:5–138:19 (Noecker).) The high incidence of allergy in patients limited the use of 0.2% brimonidine, in particular, because once a patient developed the allergy that patient could no longer use any brimonidine product to lower IOP. (*Id.*)

74. The reduction in allergy in patients taking Combigan® compared to brimonidine three times daily was unexpected, and was not due to the reduction in brimonidine dosing from three times daily to twice daily because the dose reduction was not shown to significantly reduce the allergy rate. (PTX-034-0012 (finding that brimonidine dosed twice daily and three times daily had similar adverse event profiles).) Instead, the significant allergy reduction, which came as a surprise to the inventors, appears to be attributable to combining brimonidine and timolol into a single, fixed-combination formulation. (Trial Tr., Day 2 PM at 176:16–177:18 (Noecker).)

75. Data from across several different studies demonstrates that the allergy rate for Combigan®, approximately 5%, is far lower than prior data reported in studies that looked at the allergy rates for twice daily and three times daily brimonidine. (Trial Tr., Day 2 PM at 173:23–

176:21 (Noecker).) The prior reported rates for twice daily and three times daily brimonidine are generally similar and more than double the rate found for Combigan® in the pivotal 12T and 13T studies. (*Id.*; PTX-54-0003 (reporting 12.7% allergy rate for twice daily brimonidine); PTX-55-0006 (reporting 15.7% allergy rate with three times daily brimonidine); PTX-70-0007 (reporting 5.2% allergy rate for twice daily Combigan®).)

76. And as discussed above, 0.2% brimonidine dosed twice per day and 0.2% brimonidine dosed three times per day were shown to have similar adverse event rates. (DTX-1110 at S24–S25; Trial Tr., Day 2 PM at 17:24–18:8 (Samples); PTX-034-0012 ("the profile and incidence of ocular and systemic adverse events are similar with twice-daily and 3-times-daily administration"); Trial Tr., Day 2 PM at 150:2-151:8 (Noecker).) A later clinical study comparing Combigan® to brimonidine 0.2% monotherapy dosed twice a day further confirmed that the allergy reduction is not due to removing the third dose of brimonidine. As reported by Motolko, this study showed that the allergy rate in patients taking Combigan® twice per day was 50% lower than the allergy rate experienced by patients taking 0.2% brimonidine dosed twice per day:

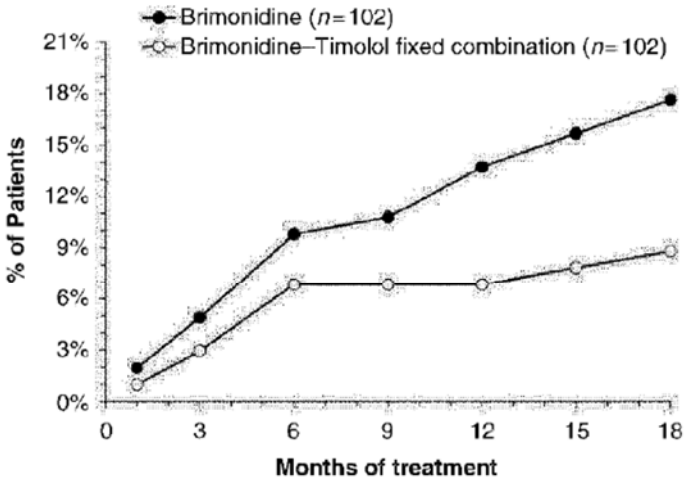


Figure 1. *Percentage of patients who developed an ocular allergy within 1, 3, 6, 9, 12, 15, and 18 months of treatment.*

(PTX-061-0003; Trial Tr., Day 2 PM at 177:19–179:9 (Noecker).)

77. While the precise mechanism of how Combigan® reduces the incidence of ocular allergy is unknown even today, the most likely explanation is that the presence of timolol in a fixed solution protects the ocular tissues from the allergic effects of brimonidine. (Trial Tr., Day 2 PM at 176:22–177:18 (Noecker).) This synergistic effect between brimonidine and timolol was unexpected. (Trial Tr., Day 2 PM at 181:13–182:2 (Noecker); Trial Tr., Day 1 AM at 81:3–12 (Batoosingh).)

78. In addition to a lower incidence of ocular adverse events such as allergy, patients treated with Combigan® had significantly fewer incidences of nervous system side effects when taking Combigan® compared to brimonidine three times daily. For example, they experienced less somnolence (i.e., sleepiness) and oral dryness. (PTX-013F at AGN_COMBI0006288-90; Trial Tr., Day 1 PM at 58:12–20, 59:23–60:10, 60:18–61:4 (Noecker); PTX070-0007; Trial Tr., Day 1 AM at 78:20-79:18, 80:22-81:2, 90:10-21 (Batoosingh).) Allergan demonstrated the significant reduction in somnolence and oral dryness as compared with adjunctive therapy using brimonidine three times daily and timolol twice daily in clinical trials 190342-023T and 190342-024T. Specifically, the 024T study found a nearly two-fold greater risk of sleepiness in patients treated with the adjunctive therapy as compared to the fixed combination. (PTX-013E at AGN_COMBI0022643.) The 024T study also showed a significant reduction in dry mouth from 24.0% in patients treated with the adjunctive therapy to 14.8% in patients treated with the fixed combination therapy. (*Id*.) Since both timolol and brimonidine cause somnolence and oral dryness, combining the two in a twice a day regimen would not be expected to reduce the number of side effects as compared to three times a day brimonidine. The comparative patient would be receiving four doses of drugs that cause those side effects—two each of brimonidine

and timolol—as opposing to only three doses of drug—brimonidine only—that causes those side effects.

79. As a result, the FDA approved Combigan® in 2007, after nearly a decade of work from Allergan, which included numerous clinical trials. (Trial Tr., Day 1 AM at 61:10–15 (Batoosingh).) When the FDA finally approved the New Drug Application ("NDA") for Combigan® in October of 2007, after several rounds of clinical studies, it was the first fixed combination glaucoma product approved in over nine years. (Trial Tr., Day 1 AM at 46:10–23 (Batooshingh).)

80. FDA approval of Combigan® was a surprise to those in the industry and to those who treat glaucoma and ocular hypertension patients. Dr. Noecker testified that, prior to seeing the clinical results, he believed Combigan® would be "a dog of a drug." (Trial Tr., Day 2 PM at 194:13–24 (Noecker).) He was "pleasantly surprised" that Combigan® was able to fill the afternoon trough with twice a day dosing, and unexpectedly reduce the incidence of adverse events. (*Id*.)

IV. INFRINGEMENT

A. Both Combigan® And Sandoz's Proposed Product Contain 0.2% Brimonidine Tartrate and 0.68% Timolol Maleate As Ingredients, Which Reduces To 0.132% Brimonidine and 0.5% Timolol

81. The asserted claims of the '149 and '976 patents require 0.2% weight percent brimonidine and 0.5% weight timolol as ingredients where "brimonidine" includes the chemical compound brimonidine, including its free base and salt forms and "timolol" means the chemical compound timolol, including its free base and salt forms.

82. Combigan® contains 0.2% brimonidine tartrate and 0.68% timolol maleate as ingredients, as reflected in Allergan's NDA for Combigan® and by expert testimony at trial. (*See, e.g.*, PTX 013J at 55343; Trial Tr., Day 1 PM at 75:9–11, 79:4–13, 85:3–6 (Noecker); Trial

Tr., Day 1 PM at 159:2–11 (Tanna).) Although there are some documents that refer to Combigan® using 0.5% timolol maleate (*see, e.g.*, PTX 070 at 1231), Allergan's own expert admitted that references to Combigan® using 0.5% timolol maleate are either "loose language" or a "mistake." (Trial Tr., Day 1 PM at 76:24–77:5 (Noecker).)

83. There is no serious dispute that Sandoz's proposed product uses the same ingredients as Combigan®. (PTX 016B at 357; PTX 015A at 771.)

84. To determine the weight percentages of the timolol and brimonidine individually for Combigan®, rather than considering the weight percent of the salt ingredients as a whole (i.e., timolol maleate and brimonidine tartrate), one could and should subtract the weight of the acids from each salt. (Trial Tr., Day 1 PM at 161:20–162:17 (Tanna).) This exercise should apply to both timolol maleate and brimonidine tartrate. (Trial Tr., Day 1 PM at 87:21–24 (Noecker); Trial Tr., Day 1 PM at 162:25-163:7 (Tanna).)

85. Expert testimony confirmed that after subtracting the maleic acid from timolol maleate, the weight of timolol in Combigan® (and, thus, Sandoz's proposed product) is 0.5%. (Trial Tr., Day 1 PM at 85:17–86:4, 86:9–17, 88:5–10 (Noecker); Trial Tr., Day 1 PM at 161:20–162:10 (Tanna).)

86. Expert testimony confirmed that after subtracting the tartaric acid from brimonadine tartrate, the weight of brimonidine in Combigan® (and, thus, Sandoz's proposed product) is 0.132%. (Trial Tr., Day 1 PM at 88:11–15 (Noecker).)

87. The prosecution history for the '149 patent further confirms these mathematical calculations for brimonidine tartrate and timolol maleate. (PTX 002 at 278 (footnotes a and b in composition table).)

88. Accordingly, Sandoz's proposed product and Combigan® contain 0.2% brimonidine tartrate, which reduces to 0.132% brimonidine, and not 0.2% brimonidine as the claims of the '149 and '976 patents require. (Trial Tr., Day 1 PM at 162:11–17 (Tanna).) Similarly, Sandoz's proposed product and Combigan® contain 0.68% timolol maleate, which reduces to 0.5% timolol. (Trial Tr., Day 1 PM at 85:17–86:4, 86:9–17, 88:5–10 (Noecker); Trial Tr., Day 1 PM at 161:20–162:10 (Tanna).)

B. Both Combigan® and Sandoz's Proposed Product Reduce the Incidence of Adverse Events

1. Sandoz's Proposed Product Will Be Clinically Identical to Combigan®

89. As discussed above, there is no serious dispute that Sandoz's proposed product uses the same ingredients as and is chemically identical to Combigan®, and thus will perform the same as Combigan®. As an initial matter, Sandoz submitted a biowaiver to FDA, exempting it from performing any clinical or bioequivalence studies on their product. (PTX-16D.) In its biowaiver, Sandoz stated that "in vivo bioavailability or bioequivalence may be considered self-evident based on the data supplied in the application[.]" (PTX-16D at SAN-BRI-00063; *see also* Trial Tr., Day 1 PM at 51:20–24 (Noecker) (stating that the biowaiver "confirms that the proposed drug is a copy of Combigan®, is identical and would perform identical in terms of efficacy").) And Sandoz's expert, Dr. Tanna, testified that "the Sandoz product will be bioequivalent to Combigan®," and "the Sandoz product will act the same as Combigan®." (Trial Tr., Day 2 AM at 34:4-10 (Tanna).)

90. Dr. Mittleberg, Sandoz's Vice President of Product Development, agreed, testifying that Sandoz's proposed product would be "therapeutically equivalent to Combigan®," that it "will lower intraocular pressure to the same extent Combigan® does," that it will "have the same side effect profile as Combigan® does," and that "there will effectively be no

differences in clinical performance – in clinical performance between its product and Combigan®." (Trial Tr., Day 1 PM at 14:15–15:10 (Mittleberg); Trial Tr., Day 1 PM at 16:13–17:1) (Ramirez) ("Q: So you'd expect the same IOP-lowering between Combigan® and Alcon's ophthalmic product? A: It would be equivalent, yes.").)

91. Sandoz does not dispute that its proposed product will perform the same as Combigan®, and offered no evidence to the contrary. Therefore, the Court finds that Sandoz's Proposed Product will perform the same as Combigan®, as to the reduction of adverse events.

2. Sandoz's Proposed Product Will Reduce Adverse Events as Compared to Brimonidine 0.2% Administered Three Times

92. Sandoz does not challenge Allergan's contention that its proposed product will meet the reduction in side effect limitations of the claims of the '425 patent. For the reasons discussed below, the Court finds that Sandoz's proposed product meets those limitations.

93. First, the data Allergan generated in the 12T and 13T clinical studies shows that the incidence of each of the claimed adverse events is lower in patients receiving Combigan® than in patients receiving 0.2% brimonidine administered three times daily. Specifically, Allergan pooled the 12 month results of those two clinical studies in the "Summary of Clinical Safety," which was submitted to FDA as part of Allergan's NDA on Combigan®. (PTX-13F.) The data for each of the claimed adverse events is summarized below:

	Combigan® BID	Brimonidine 0.2% TID	Timolol 0.5% BID
Oral Dryness	8 (2.1%)	36 (9.4%)	2 (0.5%)
Somnolence	6 (1.6%)	15 (3.9%)	2 (0.5%)
Conjunctival Hyperemia	66 (17.1%)	90 (23.6%)	31 (7.9%)
Eye Pruritus	22 (5.7%)	47 (12.3%)	15 (3.8%)
Allergic Conjunctivitis	20 (5.2%)	37 (9.7%)	2 (0.5%)
Conjunctival Folliculosis	19 (4.9%)	35 (9.2%)	7 (1.8%)
Foreign Body Sensation	8 (2.1%)	19 (5.0%)	7 (1.8%)

(PTX-13F at AGN_COMBI0006288-90.) Each of those reductions was statistically significant. (*Id*.; *see also* PTX-13F at AGN_COMBI0006283-84 ("The rate was significantly lower in 5 of these 8 adverse events including: conjunctival hyperemia, eye pruritus, allergic conjunctivitis, conjunctival folliculosis, and foreign body sensation (Tables 2.7.4.2-1 and 2.7.4.2-3). In addition, for individual systemic adverse events in the pooled 12-month data, the incidence of somnolence and oral dryness were statistically significantly lower with combination treatment than with brimonidine (Table 2.7.4.2-3).").)

94. Other reports of the data from the 12T and 13T clinical studies further show that the rate of the claimed adverse events with treatment with twice-per-day Combigan® is lower than three-times-per-day brimonidine 0.2%. (*See* PTX-13A at AGN_COMBI0007714; PTX-13L at AGN_COMBI0060050; PTX-1 at 7:22–37; Trial Tr., Day 1 PM at 58:3–62:22.)

95. As discussed above, Sandoz's proposed product will perform the same as Combigan® does with respect to adverse events. (*See* Trial Tr., Day 1 PM at 15:2-5 (Mittleberg); Trial Tr., Day 1 PM at 63:5-8 (Noecker).)

96. For all of these reasons, the Court finds that the use of Sandoz's proposed product will meet each of the limitations of claims 1–8 of the '425 patent.

3. Sandoz's Knowledge and Intent that the Proposed Product Be Used to Infringe the '425 Patent

97. For the reasons discussed below, the Court finds that Sandoz knows and intends that its proposed product will be used to infringe the asserted claims.

98. Sandoz has admitted that it had knowledge of the patents-in-suit, at least as of the date on which the patents were listed in the Orange Book. (C.A. No. 2:15-cv-347, Dkt. 14 at ¶¶ 44, 52, 71, 79, 138, 146.)

99. Sandoz encourages doctors and patients to use their proposed product in an infringing manner. Sandoz's label instructs doctors and patients to administer their drug twice per day to ocular hypertension patients. (PTX-16A at SDZ(33)0003361; Trial Tr., Day 1 PM at 66:5-15 (Noecker).)

100. Moreover, when compared with the label on Sandoz's 0.2% brimonidine product, the label on Sandoz's proposed product reflects the reduction in adverse events. (*Compare* PTX-16A *with* PTX-366.) The label on Sandoz's proposed product states that "[i]n clinical trials of 12 months duration with brimonidine tartrate and timolol maleate ophthalmic solution," that the claimed adverse events of allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, and eye pruritus occurred in approximately 5% to 15% of patients, while the claimed adverse events of foreign body sensation, oral dryness, and somnolence occurred in 1% to 5% of patients. (PTX-16A at SDZ(33)0003363.) In comparison, the label on Sandoz's 0.2% brimonidine product reports that each of the claimed adverse events occurred in 10%-30% of patients. (PTX-366; Trial Tr., Day 1 PM at 136:14–137:1 (Herrick).)

101. Sandoz's Vice President of Product Development, Dr. Mittleberg, testified that Defendants intend for patients to use its proposed product as instructed on the package insert. (Trial Tr., Day 1 PM at 11:22–13:1 (Mittleberg) ("Question: Does Sandoz intend that patients would use their product in compliance with that instruction? Answer: If that was our labeling, that's the intent.")

102. Furthermore, Sandoz knows and intends that its proposed product will be used by patients with glaucoma in addition to patients with ocular hypertension. Mr. David Herrick, the Executive Director of Ophthalmic and Otic for Sandoz, testified that Sandoz will seek to switch patients from Combigan® to Sandoz's proposed product, without regard to indications on the

label. (Trial Tr., Day 1 PM at 130:1–132:6 (Herrick).) Further, because Sandoz's proposed product is therapeutically equivalent to Combigan®, retailers and wholesalers will be able to use it as a substitute for Combigan®. (Trial Tr., Day 1 PM at 131:21–132:6 (Herrick); Trial Tr., Day 1 PM at 69:11-70:5 (Noecker); Trial Tr., Day 2 AM at 30:17–23 (Tanna).) All of the experts in the case agreed that there is no product on the market that is for the treatment of glaucoma but not ocular hypertension, or ocular hypertension but not glaucoma. (Trial Tr., Day 1 PM at 34:16-23 (Noecker); Trial Tr., Day 2 AM at 30:5-16 (Tanna); Trial Tr., Day 2 PM at 35:10–17 (Samples).)

103. For these reasons, the Court finds that Sandoz knows and intends that its proposed product will be used to infringe claims 1–8 of the '425 patent.

4. Sandoz's Proposed Product is a Material Part of Allergan's Invention with No Substantial Non-Infringing Uses

104. There is no non-infringing use for Sandoz's proposed product, and Sandoz has offered none. Further, the Court finds that Sandoz's proposed product, which is the formulation that would be used to directly infringe the asserted claims of the'425 patent, is a material part of Allergan's invention claimed in the '425 patent. (Trial Tr., Day 1 PM at 68:5–11 (Noecker).)

V. INVALIDITY

A. Obviousness of the Patents-In-Suit

105. As discussed in greater detail above, a person of skill in the art would have expected that a twice-daily dosed fixed combination of brimonidine and timolol would be less effective in the afternoon than brimonidine 0.2% dosed three times per day. Further, a person of skill in the art would have expected the individual side effects to be exacerbated, not reduced, by such a combination. However, Allergan achieved equivalent or better IOP lowering efficacy with Combigan® than with brimonidine 0.2% dosed three times daily. Additionally, Allergan

achieved a lower incidence of adverse events experienced by patients taking Combigan® than by patients taking brimonidine 0.2% given three times daily. These unexpected results are disclosed and claimed in the asserted claims of the ’149 and ’425 patents. In addition, the ’976 method patent is supported by these unexpected results. While the Federal Circuit has previously held that the combination of brimonidine and timolol claimed in the ’463 patent is invalid as obvious, it also held that the ’149 patent’s clinical limitation covering the administration of the fixed combination “without loss of efficacy” is not obvious in light of the prior art. Similarly, as will be discussed in detail below, the Court here finds that none of Sandoz’s prior art, alone or in combination, teaches or suggests that a fixed combination of brimonidine and timolol would have been able to achieve the clinical limitations claimed in the patents-in-suit.

1. The Federal Circuit Concluded that a Fixed Combination of 0.2% w/v Brimonidine and 0.5% w/v Timolol is Obvious

106. As an initial matter, the Court notes that the Federal Circuit previously concluded that the claims of the ’463 patent were invalid as obvious. *Allergan,* 726 F.3d at 1288. Claims 1 and 4 of the ’463 patent cover the same fixed combination claimed in the ’149 and ’976 patents.

107. Claim 1 of the ’463 patent reads: “A composition comprising about 0.2% timolol by weight and about 0.5% brimonidine by weight as the sole active agents, in a single composition.” (DTX 1005 at 9:11–13.) Claims 2 and 3 further limit claim 1 by adding a limitation requiring that the composition comprise 0.001% to 0.01% benzalkonium chloride (claim 2) and 0.005% benzalkonium chloride (claim 3). (DTX 1005 at 9:14–17.)

108. Claim 4 of the ’463 patent reads: “An article of manufacture comprising packaging material and a composition within said packaging material, wherein said composition comprises about 0.2% timolol by weight and about 0.5% brimonidine by weight, in a single composition, and wherein said packaging indicates that the composition is useful for treating

glaucoma or ocular hypertension by twice a day topical administration of the composition to a person's eye." (DTX 1005 at 10:1-9.) Claims 4 and 5 further limit claim 4 by adding a limitation requiring that the composition comprise 0.001% to 0.01% benzalkonium chloride (claim 5) and, more specifically, 0.005% benzalkonium chloride (claim 6). (DTX 1005 at 10:10–15.)

109. In finding the claims of the '463 patent obvious, the Federal Circuit relied on the teachings of U.S. Patent No. 5,502,052 ("DeSantis"), "which teaches fixed combinations of alpha2-agonists and beta-blockers [including timolol] for the treatment of glaucoma." *Allergan*, 726 F.3d at 1289. The Federal Circuit further noted that DeSantis incorporates by reference a publication by Timmermans, which discloses both brimonidine and its tartrate salt. *Id*. at 1290. The Federal Circuit also relied on the teachings of Larsson, which disclosed the serial or concomitant administration of 0.2% brimonidine and 0.5% timolol. *Id.*

110. The Federal Circuit also found that brimonidine was one of three known pharmaceutically acceptable alpha2-agonists as of the time of Allergan's invention, that brimonidine was the only one available in the United States for chronic use, and that "there were at least four other fixed combination products for the treatment of ocular hypertension and glaucoma on the market at the time of the invention." *Id*.

111. In its obviousness analysis, the Federal Circuit stated that "DeSantis provides an express motivation to combine alpha2-agonists and beta blockers in order to increase patient compliance," and that "it was common at the time of the invention to provide brimonidine and timolol to a patient in serial fashion and DeSantis taught that by combining drugs in a fixed-combination formulation, patient compliance could be increased." *Id*. at 1291–92.

Therefore, the Court concluded that the claims of the ’463 patent are invalid as obvious. *Id*. at 1293.

112. The Federal Circuit’s conclusions concerning the obviousness of the ’463 claims apply with equal force to the composition elements of the asserted claims in this case. Sandoz offered evidence that these elements are the same, and Allergan’s expert, Dr. Noecker, agreed. (Trial Tri., Day 3 AM at 10:6–11:3 (Nocker).) Accordingly, because the composition limitation of the patents-in-suit is obvious, there must be some additional limitation in each of the patents-in-suit which is not obvious in order for the Court to find that the patents-in-suit are not obvious.

2. Sandoz’s Prior Art Fails to Teach or Suggest the Claimed Clinical Limitations

113. In addition to the composition limitation, each of the patents-in-suit contains clinical limitations. For example, claim 4 of the ’149 patent covers the improvement in the prior three times a day brimonidine monotherapy “without loss of efficacy” whereby brimonidine is combined with timolol in twice daily dosing. (PTX-1 at 10:10–17.) The ’976 patent claims a method of treating glaucoma or ocular hypertension with a therapeutically effective amount of a fixed combination containing 0.2% brimonidine tartrate and 0.5% timolol administered twice a day. (PTX-3 at 10:13–19.) Claim 1 of the ’425 patent recites a method of administering a fixed combination containing 0.2% brimonidine tartrate and 0.5% timolol free base administered twice a day, where the method reduces the incidence of certain adverse events compared to administration of three times a day 0.2% brimonidine tartrate monotherapy. (PTX-11 at 9:8–18.) Claims 2–8 each depend from claim 1, and each covers the reduction of a specific adverse event. (PTX-11 at 9:19–32.)

a. DeSantis

114. Just as it was in *Allergan I*, Sandoz's primary prior art reference is DeSantis, U.S. Patent No. 5,502,052. (DTX-1051.)

115. DeSantis, along with the Timmermans chapter that it incorporates by reference, discloses fixed combinations of beta blockers and alpha agonists, listing as possible examples every possible beta blocker and every possible alpha agonist. As discussed above, while the Federal Circuit previously found that composition claims directed to a general formulation of 0.2% brimonidine and 0.5% timolol were obvious over DeSantis in combination with other art, the claims at issue here are not composition claims. Rather, they are method of treatment claims, which have specific limitations as to the required efficacy and side effects of the brimonidine/timolol fixed combination. As the Federal Circuit has already found, and Sandoz's experts acknowledged at trial, DeSantis does not disclose any clinical data about any of the combinations that it proposed. (*Allergan*, 726 F.3d at 1294; Trial Tr., Day 2 AM at 53:15–54:20 (Tanna) (admitting that "there's no clinical data in this example or anywhere else in DeSantis"); Trial Tr., Day 2 PM at 11:11–15 (Samples) (admitting that the Federal Circuit found that "DeSantis did not provide clinical data on any of the possible combinations it disclosed").)

116. In particular, DeSantis does not contain any clinical data about the IOP-lowering effect of any of its proposed combination products, let alone any clinical data about whether the IOP-lowering effect of the fixed combination of brimonidine and timolol dosed twice daily would be as good as brimonidine monotherapy dosed three times daily. (Trial Tr., Day 2 PM at 156:21–24 (Noecker).) Indeed, the Federal Circuit expressly found, as Dr. Tanna admitted, that "[e]ven if we accept that this generalized teaching of DeSantis is true for all fixed combination products, we cannot equate a greater reduction in intraocular pressure with 'no loss of efficacy' as required by claim 4." (*Allergan*, 726 F.3d at 1294; Trial Tr., Day 2 AM at 53:15–54:3

(Tanna).) Therefore, DeSantis does not teach the "no loss of efficacy" limitation in claim 4 of the '149 patent. Nor does it teach the limitation of claim 1 of the '976 patent requiring therapeutic efficacy with twice-daily dosing.

117. With respect to adverse events, Dr. Samples, Sandoz's only expert to testify on the validity of the '425 patent, admitted that "DeSantis doesn't disclose any reduction in adverse events that could be gained by administering the fixed combinations." (Trial Tr., Day 2 PM at 10:13-11:6 (Samples); 156:25–157:2 (Noecker).) Consequently, DeSantis does not teach the limitations of the '425 patent requiring that the brimonidine/timolol fixed combination dosed twice daily reduce adverse events as compared to brimonidine alone dosed three times daily.

b. Larsson

118. Like DeSantis, Sandoz relied on Larsson in *Allergan I*, and the Federal Circuit addressed it in its opinion concluding claim 4 of the '149 patent to be not obvious. In this instance, Sandoz relies on the Larsson reference combined with DeSantis, using Larsson as an example of prior art showing serial or adjunctive administration of brimonidine and timolol, in other words the administration of the two drugs in separate bottles. (Trial Tr., Day 2 AM at 54:21–55:14 (Tanna).) However, the patents-in-suit disclose the prior serial use of brimonidine and timolol in the specification, and such prior serial use was addressed by the Federal Circuit on appeal. (PTX-1-001, 1:9–12 ("Such combinations or formulations are available for separate use in the ophthalmic art and have been combined in serial application during the course of treatment of glaucoma"); Trial Tr., Day 2 AM at 55:15-56:11 (Tanna).) Further, the Larsson reference itself was before the PTO during prosecution of the patents-in-suit, so the examiner had the opportunity to review it before allowing the claims. (Trial Tr., Day 2 PM at 159:13–24 (Noecker).) Given that the PTO has already allowed the claims over this reference, Sandoz faces a heightened hurdle to show invalidity over Larsson.

119. Larsson discloses a study in which healthy volunteers received three doses of brimonidine and timolol in separate bottles over a period of a day and half. (DTX-1121 at 492; Trial Tr., Day 2 AM at 56:12-58:10 (Tanna); Trial Tr., Day 2 PM at 157:18–158:14 (Noecker).) The healthy volunteers had no eye disease and were an average age of 30 years old, which is substantially younger than the average age of a glaucoma or ocular hypertension patient. (Trial Tr., Day 2 AM at 57:5–15 (Tanna); Trial Tr., Day 2 PM at 157:21–24 (Noecker).) As Dr. Noecker explained, because of its design the Larsson study teaches a person of skill in the art nothing about long-term efficacy in glaucoma and ocular hypertension patients. This fact is important because glaucoma and ocular hypertension are "chronic disease[s]" that have to be "managed over decades." (Trial Tr., Day 2 PM at 158:15–24 (Noecker).)

120. Since the study was performed in healthy volunteers, the disclosure in Larsson does not tell a person of skill in the art how brimonidine and timolol in a fixed combination would lower IOP in glaucoma and ocular hypertension patients. (Trial Tr., Day 2 PM at 158:15–159:3 (Noecker).) Moreover, it fails to show whether such a fixed combination dosed twice daily would perform without loss of efficacy as compared to brimonidine alone dosed three times daily. (Trial Tr., Day 2 PM at 158:25–159:7 (Noecker).)

121. The IOP measurements in Larsson strongly suggest that adding timolol to brimonidine would not be enough to overcome the more than 3 mmHg loss of efficacy seen with twice-daily brimonidine. Table 2 of Larsson shows that, at 4:00 P.M., the IOP reading for brimonidine alone was 9.4 mmHg, and the reading for timolol added to brimonidine was 7.7 mmHg. (DTX-1121 at 494.) Thus, the benefit of adding timolol to brimonidine in the Larsson study was only 1.7 mmHg. (*Id.*) That would not be enough to bridge the 3.25 mmHg afternoon trough between twice-daily and three times daily brimonidine. (Trial Tr., Day 2 AM at 59:1–

60:10 (Tanna).) Based on that data, the Court determines that a person of skill in the art reading Larsson would not expect that a fixed combination of brimonidine and timolol dosed twice daily would be able to maintain IOP-lowering efficacy as compared to brimonidine alone dosed three times a day. Instead, the data in Larsson teaches away from being able to achieve the clinical results recited in claim 4 of the '149 patent.

122. Moreover, there is no mention of the evaluation of side effects in Larsson. Consequently, it discloses nothing about whether the combination of brimonidine and timolol, in a fixed or unfixed combination, dosed twice daily would reduce adverse events as compared to brimonidine alone dosed three times daily. (Trial Tr., Day 2 PM at 159:8–12 (Noecker).)

123. For these reasons, the Court finds that Larsson does not teach any of the claim limitations that were missing in the DeSantis reference. Accordingly, Larsson does not render the claims of the patents-in-suit obvious when combined with DeSantis.

c. Other Adjunctive Therapy References: Stewart, Arici, and Yuksel

124. Defendants cite three additional references that discuss adjunctive therapy with brimonidine and timolol, but, like Larsson, the Court finds that they also do not teach or suggest the treatment-related limitations of the asserted claims.

125. Stewart examined the addition of latanoprost, brimonidine, or dorzolamide in patients already taking a beta blocker like timolol. (DTX-1320 at DEFS(B/T) 000433.) It concluded that latanoprost was the best for both efficacy and side effects in adjunctive use. (DTX-1320; Trial Tr., Day 2 PM at 160:2–25 (Noecker).) Stewart does not report data at any specific time point, so it does not speak to how brimonidine added to timolol lowers IOP at the afternoon trough, let alone how it would do so in a fixed combination as opposed to the adjunctive therapy examined in Stewart. (Trial Tr., Day 2 PM at 161:1–25 (Noecker).) Nor does

Stewart say anything to suggest that adding brimonidine to timolol would reduce side effects as compared to brimonidine alone. (Trial Tr., Day 2 PM at 162:1–3 (Noecker).)

126. The Arici reference was not published until January 2002. (DTX-1125 at DEFS(B/T) 000171.) The patents-in-suit were filed in April 2002, but because Arici was published less than a year before that, the inventors submitted a declaration during prosecution to swear behind Arici based on prior invention. (Trial Tr., Day 2 PM at 24:11–26:7 (Samples); PTX-2-000274; Trial Tr., Day 2 PM at 162:7-11; 162:25–163:8 (Nocker).) Thus, the Court concludes that Arici is not prior art as to the patents-in-suit.

127. Even if Arici were prior art, it similarly does not teach or suggest the clinical limitations of the asserted claims. Arici discloses a short-term study in twenty patients, where brimonidine 0.2% was given twice per day to patients who were not achieving sufficient IOP-lowering on timolol alone. (DTX-1125 at DEFS(B/T) 000173.) There is no data in Arici about IOP-lowering on brimonidine alone, either twice or three times per day. (DTX-1125.) Additionally, Arici discusses nothing about adverse ocular events, or about the systemic adverse events of somnolence or oral dryness. (Trial Tr., Day 2 PM at 162:12–22 (Noecker).) Thus, it teaches a person of skill in the art nothing about what impact, if any, a fixed combination of brimonidine and timolol would have on adverse events as compared to brimonidine alone. (*Id.*)

128. As to Yuksel, this reference was also before the PTO during prosecution of all the patents-in-suit. (Trial Tr., Day 2 PM at 165:5–19 (Noecker).) Like Larsson, Yuksel is a short term study that lasted only two days. (DTX-1127.) Patients already on timolol received a single drop of brimonidine to measure any effect on IOP. (DTX-1127 at DEFS(B/T) 000196; Trial Tr., Day 2 PM at 163:20–164:11 (Noecker).) It teaches nothing about long-term efficacy for treatment of glaucoma or ocular hypertension. It teaches nothing about combining brimonidine

and timolol into a fixed combination, and it teaches nothing about the efficacy of such a combination. (Trial Tr., Day 2 PM at 164:5–165:3.) Like Arici, it makes no mention of the claimed adverse ocular events, or of the claimed adverse events of somnolence or dry mouth. (*Id.*) It therefore teaches nothing to a person of skill in the art about what effect, if any, a fixed combination of brimonidine and timolol would have on the claimed adverse events as compared to brimonidine alone.

129. For these reasons, the Court determines that none of the adjunctive therapy references—Stewart, Arici, and Yuksel—teach or suggest the claimed clinical limitations of the patents-in-suit.

d. Art on Other Fixed Combinations Teaches Away from Achieving the Clinical Limitations of the Claims

130. In addition to the art related to adjunctive therapy with brimonidine and timolol, Sandoz also relied on art related to other fixed combination products, particularly Cosopt®, which is a fixed combination of dorzolamide and timolol. This art relating to other fixed combination products was also before the district court and Federal Circuit in *Allergan I*. *Allergan*, 726 F.3d at 1290.

131. Dr. Tanna testified that Cosopt® is an "excellent analogy" for the brimonidine/timolol fixed combination because "[d]orzolamide was FDA-approved as a three-times-a-day drug. In reality, we were using it twice a day. And timolol was approved as a twice-a-day drug. We were using it, for the most part, twice a day. And Cosopt® was a twice-a-day drug with both agents in the same bottle." (Trial Tr., Day 1 PM at 156:20–157:4 (Tanna).) So, like Combigan®, Cosopt® combined one drug approved for three times daily dosing with one drug approved for twice-daily dosing into a fixed combination for twice-daily dosing. However,

Cosopt® does not suggest that the specific clinical limitations of the asserted claims could be achieved by making such a combination. Instead, it suggests just the opposite.

132. The Clineschmidt paper (DTX-1169) relied on by Sandoz compared Cosopt® dosed twice daily with dorzolamide monotherapy dosed three times daily and timolol monotherapy dosed twice daily. (Trial Tr., Day 2 PM at 166:3–15 (Noecker).) It reports IOP measurements for Hour 0, which is the time of dosing, and Hour 2, which "is at peak or best eye-pressure lowering time." (DTX-1169 at DEFS(B/T) 000028; Trial Tr., Day 2 PM at 166:17-23 (Noecker); *see also* at 132:24-133:16 (Noecker).) The study does not report any IOP measurements in the afternoon. (Trial Tr., Day 2 PM at 166:24–167:24 (Noecker).) Although there is no reported data for the afternoon, the data for Hour 2 provides information to a person of skill in the art about the IOP-lowering efficacy that timolol adds to dorzolamide. (DTX-1169 at Table 3; Trial Tr., Day 2 PM at 167:25–169:2 (Noecker).) At the Hour 2 time point, timolol adds a maximum of 2.4 mmHg in IOP-lowering effect to dorzolamide, calculated by taking the IOP lowering for dorzolamide alone compared to the IOP lowering for the dorzolamide/timolol fixed combination:

Table 3. Intraocular Pressure Summary Statistics*: Mean (Standard Deviation)

Examination	Treatment	N	Baseline	Treatment	Change	Percent Change
Hr 0						
Wk 2	Combination	99	25.5 (3.4)	22.6 (3.4)	−2.9 (3.3)	−10.9 (11.7)
	Dorzolamide	51	25.5 (3.8)	23.7 (3.6)	−1.9 (3.4)	−6.6 (12.3)
	Timolol	96	25.3 (3.2)	23.9 (4.2)	−1.4 (3.2)	−5.4 (11.6)
Mo 1	Combination	102	25.5 (3.4)	22.5 (3.5)	−3.0 (3.4)	−11.3 (12.5)
	Dorzolamide	51	25.5 (3.8)	23.7 (4.0)	−1.8 (3.9)	−6.3 (14.2)
	Timolol	98	25.2 (3.1)	23.3 (4.4)	−2.0 (3.0)	−7.9 (11.2)
Mo 2	Combination	102	25.5 (3.4)	22.6 (3.8)	−2.9 (3.1)	−11.0 (11.9)
	Dorzolamide	51	25.5 (3.8)	23.8 (4.2)	−1.8 (4.3)	−6.0 (16.5)
	Timolol	98	25.2 (3.1)	23.3 (4.2)	−1.9 (3.1)	−7.5 (11.9)
Mo 3	Combination	102	25.5 (3.4)	22.7 (3.9)	−2.8 (3.4)	−10.6 (12.5)
	Dorzolamide	51	25.5 (3.8)	24.2 (5.1)	−1.4 (4.3)	−4.9 (16.7)
	Timolol	98	25.2 (3.1)	23.6 (4.3)	−1.7 (3.1)	−6.7 (11.9)
Hr 2						
Wk 2	Combination	100	25.0 (4.0)	21.0 (4.0)	−4.0 (3.1)	−15.8 (11.4)
	Dorzolamide	51	24.7 (3.3)	21.8 (3.4)	−2.8 (3.8)	−10.8 (13.3)
	Timolol	93	24.3 (2.6)	22.4 (3.7)	−1.9 (2.5)	−8.1 (10.5)
Mo 1	Combination	103	25.0 (3.9)	20.7 (4.3)	−4.4 (3.0)	−17.3 (11.5)
	Dorzolamide	51	24.7 (3.3)	22.4 (3.8)	−2.3 (4.5)	−8.5 (16.4)
	Timolol	95	24.3 (2.6)	22.3 (4.6)	−2.0 (3.3)	−8.7 (13.4)
Mo 2	Combination	103	25.0 (3.9)	20.6 (4.2)	−4.4 (3.3)	−17.1 (12.5)
	Dorzolamide	51	24.7 (3.3)	21.2 (3.5)	−3.5 (4.3)	−13.3 (15.5)
	Timolol	95	24.3 (2.6)	22.0 (4.2)	−2.4 (3.2)	−9.8 (13.2)
Mo 3	Combination	103	25.0 (3.9)	20.7 (4.5)	−4.4 (3.3)	−17.3 (12.9)
	Dorzolamide	51	24.7 (3.3)	22.7 (3.8)	−2.0 (4.1)	−7.4 (15.8)
	Timolol	95	24.3 (2.6)	22.8 (4.6)	−1.6 (3.7)	−6.6 (15.3)

* All patients treated analysis (last observation carried forward) — worse eye.

(DTX-1169 at Table 3.) As Dr. Noecker explained, that amount of additional IOP lowering would not be enough to make up for the afternoon trough experienced with twice daily brimonidine:

> Q: And Dr. Noecker, remind the Court how big was that gap in IOP-lowering efficacy between twice-a-day brimonidine and three-times-a-day brimonidine that we need timolol to fill.
> A: About 3-1/2 millimeters of mercury.
> Q: So in this [Clineschmidt] study, is the timolol adding enough to make up for that gap?
> A: No. The best it does, even, once again, in this best-case-scenario time point, is about 2.4.

(Trial Tr., Day 2 PM at 168:15–168:23 (Noecker); *see also* at 132:9–133:23 (Noecker).) Thus, Clineschmidt does not teach a person of skill in the art that a fixed combination of brimonidine and timolol dosed twice daily would maintain efficacy as compared to brimonidine alone dosed three times daily. Actually, Clineschmidt should make a person of skill in the art "pessimistic"

about whether timolol would add enough IOP-lowering efficacy to brimonidine to make up the afternoon gap and therefore teaches away. (Trial Tr., Day 2 PM at 169:3–9 (Noecker).)

133. Additionally, Clineschmidt does not show an improved side effect profile for the fixed combination of dorzolamide and timolol dosed twice daily as compared to dorzolamide alone dosed three times daily. (DTX-1169 at DEFS(B/T)00031-32.) As a result, Clineschmidt does not suggest to a person of skill in the art that a fixed combination of brimonidine and timolol dosed twice daily would reduce side effects as compared to brimonidine alone dosed three times daily.

134. Sandoz also relied on the Airaksinen reference (DTX-1331), which addresses a fixed combination of timolol and pilocarpine known as Timpilo. (Trial Tr., Day 2 PM at 169:16–22 (Noecker).) As Dr. Noecker explained, the Timpilo fixed combination was never approved in the U.S. because it "failed to meet the bar for clinical utility," meaning that "the side-effect profile was largely unacceptable to many patients, and the ability to control IOP in a consistent fashion was suboptimal." (Trial Tr., Day 2 PM at 169:20–170:7 (Noecker).) The IOP-lowering graphs in Airaksinen reference support this testimony, demonstrating that the IOP control with the pilocarpine/timolol fixed combination is "inconsistent." (Trial Tr., Day 2 PM at 170:8–18 (Noecker) (explaining that "pilocarpine is typically a four-times-a-day drug, so the addition of timolol did not smooth out the curve adequately"); DTX-1331 at DEFS(B/T) 000204.) Thus, Airaksinen would not suggest to a person of skill in the art that the addition of timolol to brimonidine in a fixed combination for twice-daily dosing would provide consistent IOP-lowering throughout the day or perform without loss of efficacy as compared to brimonidine monotherapy dosed three times daily. Similarly, it would not suggest that a fixed combination of

brimonidine and timolol could reduce the claimed side effects as compared to brimonidine alone dosed three times a day.

135. The Court finds that, rather than supporting Defendants' obviousness arguments, the prior art related to other fixed combinations would have suggested to a person of skill in the art that a fixed combination of brimonidine and timolol would not achieve the efficacy and side effect limitations in the asserted claims. These teach away from, not toward, the claimed limitations.

e. Prior Art on Brimonidine Monotherapy Does Not Teach or Suggest the Claimed Limitations

136. Finally, Sandoz relies on certain prior art that discusses brimonidine therapy and compares brimonidine dosing at different concentrations and different frequencies, particularly for its obviousness arguments related to the adverse event claims of the '425 patent. Again, the Court finds that this art does not teach or suggest the claimed limitations.

137. As an initial matter, Dr. Samples admitted that there is no prior art that teaches the claimed reduction in side effects of the '425 patent:

> Q: There is no piece of prior art that shows that making a fixed combination with brimonidine reduces the risk of allergy as opposed to brimonidine TID, correct?
> A: In the prior art? No. That's correct.
> Q: That is correct?
> A: Yes.

(Trial Tr., Day 2 PM at 31:3–21 (Samples); *see also* at 29:17-20 ("Q: Is there anything in the prior art that suggest that the side effects might be reduced by making the fixed combination as—as compared to the individual component drugs? A: No, not that comes to mind at the moment.").)

138. The Court finds that the evidence supports Dr. Samples' admission. There is nothing in the prior art teaching that a fixed combination of brimonidine and timolol would

reduce side effects as compared to brimonidine alone. Sandoz relied primarily on the Walters paper (DTX-1110), which discussed various studies with brimonidine, including a study of 101 glaucoma and ocular hypertension patients that compared brimonidine dosed three times daily with brimonidine dosed twice daily. (DTX-1110 at S24; Trial Tr., Day 2 PM at 12:23–13:13 (Samples).) With respect to side effects, Walters found that "[o]verall, ocular and systemic side adverse events were reported for 8% [4 out of 50] of patients in the twice-daily group, and 9.8% [5 out of 51] in the three times daily group." (DTX-1110 at S24.) The data in Walters does not break out the rates of occurrence of any individual adverse events, including any of the claimed adverse events. (Trial Tr., Day 2 PM at 14:3–17:18 (Samples).) Walters itself draws no conclusion that the adverse events were lower for the twice-daily group as opposed to the three times daily group, and Dr. Samples also acknowledged that he would not draw that conclusion based on the data in Walters:

> Q: And you wouldn't rely on this difference of one patient to draw any conclusions about the relative rates of any adverse events among twice-daily and three-times-a-day dose of brimonidine, correct?
> A: The difference is small, so I would not.

(Trial Tr., Day 2 PM at 18:4–8 (Samples).) Therefore, the Court finds that Walters does not teach the adverse event reduction limitations of the claims of the '425 patent.

139. Allergan relied on the Adkins paper (PTX-34) to support its position that the prior art found no difference in adverse event rates between twice-daily and three times daily dosing of brimonidine. Like Walters, Adkins reports on several different studies on brimonidine. First, Adkins reports on a dose response study that examined various concentrations of brimonidine, ranging from 0.08% to 0.5%. (PTX-34-0003.) Adkins concludes that side effects "are generally mild to moderate and appear to be dose related, developing more frequently among patients treated with higher doses of brimonidine." (PTX-34-0012.) The Court understands the reference

to say that "higher doses" means higher concentrations, i.e., the 0.5% concentration. (*See id.*) In contrast, when discussing the dose frequency study, which examined 0.2% brimonidine dose twice-daily versus three times daily, Adkins concludes that "the profile and incidence of ocular and systemic adverse events are similar with twice-daily and 3-times-daily administration." (PTX-34-0012; Trial Tr., Day 2 PM at 150:2–151:8 (Noecker); Trial Tr., Day 2 PM at 9:5-10:9 (Samples.).) In making that conclusion, Adkins cites to the Walters and Rosenthal papers relied on by Defendants. (PTX-34-0012, -0016; Trial Tr., Day 2 PM at 150:2–151:8 (Noecker).))

140. Based on the information in the Walters and Adkins references, and the expert testimony from Dr. Samples and Dr. Noecker, the Court finds that, prior to the patents-in-suit, a person of skill in the art would have expected a similar adverse event profile for brimonidine dosed twice versus three times-daily. (Trial Tr., Day 2 PM at 151:9–16 (Noecker) (explaining that a person skilled in the art would have expected the side effect profile for twice daily and three times daily brimonidine to be similar).) Thus, a person of skill in the art would not have expected that Combigan® would reduce the claimed adverse events as compared to brimonidine alone dosed three times daily.

3. Reduction in BAK Would Not Suggest a Reduction in Adverse Events

141. Sandoz also suggested that those of skill in the art would have expected the reduction in adverse events with the brimonidine/timolol fixed combination because the fixed combination reduced the amount of benzalkonium chloride ("BAK"), a preservative, that a patient needed to take. However, the Court finds that the evidence does not support that this reduction in BAK would have been expected to reduce the claimed adverse events.

142. The BAK preservative is present in both the Combigan® fixed combination and in brimonidine monotherapy. (Trial Tr., Day 2 PM at 3:23–4:5 (Samples).) With brimonidine

monotherapy, a patient receives three doses of BAK per day. With Combigan®, a patient receives two doses.

143. Sandoz relied on the testimony of Dr. Samples to support its argument that the reduction in BAK would have been expected to reduce certain adverse events, such as hyperemia. (Trial Tr., Day 2 PM at 5:6–21 (Samples).) However, the credibility of Dr. Samples' testimony is called into question by his prior testimony at a 2013 trial at which he stated that there was no prevailing sentiment that BAK caused hyperemia. (Trial Tr., Day 2 PM at 5:6–7:4 (Samples).) Further, Dr. Samples admitted here that BAK is not known to cause the claimed side effects or oral dryness or somnolence. (Trial Tr., Day 2 PM at 7:6–11.)

144. Dr. Noecker rebutted Dr. Samples' testimony, and explained that the difference between receiving BAK twice a day versus three times a day would not have been expected to reduce the claimed side effects because "the only thing that really seems to be the definitive thing, is to eliminate it 100 percent altogether, do not expose that person's eye at all, because even a little bit in some people, it's—it's meaningless when you go from 4 to 3 or 3 to 2." (Trial Tr., Day 3 AM at 73:3–74:2 (Noecker).)

145. The Court finds the position espoused by Dr. Noecker to be both more credible and persuasive. Accordingly, the Court finds that the reduction in BAK with the fixed combination dosed twice daily would not have been expected to reduce adverse events as compared to brimonidine monotherapy dosed three times daily.

4. The Claimed Limitations Are Not Inherent

146. Defendants also argue that they do not need to show these limitations in the prior art at all because they are simply inherent. The Court disagrees.

a. Dose Reduction Without Loss of Efficacy and Reduction of Adverse Events Is Not Inherent in All Fixed Combination

Formulations of the Claimed Brimonidine and Timolol Combinations

147. The Federal Circuit addressed inherency on appeal in *Allergan I*, finding that "[t]he evidence of record does not establish that a dose reduction 'from 3 to 2 times a day without loss of efficacy' limitation is an inherent property or a necessary result of the administration of 0.2% brimonidine and 0.5% timolol in a single composition." *Allergan*, 726 F.3d at 1294 n.1. The Federal Circuit went on to explain that "it may be true that the mere administration of 0.2% brimonidine and 0.5% timolol twice daily in any fixed combination formulation inherently produces the claimed result. Alternatively, it may be true that only certain fixed combination formulations produce this result." (*Id.*) As shown by the record in the first appeal, the Federal Circuit did not reach a conclusion in favor of either option. (*Id.*)

148. Sandoz has failed to introduce evidence under the inherency inquiry as set forth by the Federal Circuit—whether the claimed efficacy and side effect limitations would necessarily occur with all fixed combination formulations of 0.2% brimonidine and 0.5% timolol. To the contrary, Defendants' expert, Dr. Samples, admitted that the limitations would not necessarily occur in all formulations of 0.2% brimonidine and 0.5% timolol. (Trial Tr., Day 2 PM at 33:5–35:2 (Samples) ("Q: So you agree that it's possible that not only fixed combinations of .2% brimonidine and .5% timolol will give the claimed reduction in adverse events, correct? A: Correct.").) In other words, it is possible that not all fixed combinations of 0.2% brimonidine and 0.5% timolol would necessarily achieve the claimed efficacy and side effect limitations. This fact negates Sandoz's inherency argument.

b. Neither Dose Reduction Without Loss of Efficacy Nor Reduction of Adverse Events is Inherent in Prior Art Adjunctive Therapy

149. The Court has already found that the prior art does not teach that twice-daily dosing with a fixed combination of 0.2% brimonidine and 0.5% timolol would perform without loss of efficacy as compared to dosing with brimonidine monotherapy three times daily. Nor does the prior art teach that twice daily dosing with a fixed combination of 0.2% brimonidine and 0.5% timolol would reduce any of the claimed side effects as compared to dosing with 0.2% brimonidine monotherapy three times daily.

150. In support of its inherency arguments, Sandoz relies on references that its experts freely acknowledged are not prior art. (Trial Tr., Day 2 PM at 27:2-21 (Samples); Trial Tr., Day 2 AM at 28:8-23 (Tanna).) In particular, Defendants rely on clinical studies, published in the Konstas and Goni references (DTX-1397; DTX-1209) after the filing of the patents-in-suit, that compared the performance of Combigan® dosed twice daily to the adjunctive use of brimonidine and timolol in separate bottles twice daily.

151. Defendants rely on Konstas to argue that the claimed efficacy results for Combigan® were inherent in prior art twice-daily adjunctive therapy. However, other evidence at trial demonstrates that this is simply not the case—the addition of timolol does not "inherently" add enough IOP lowering to brimonidine dosed twice daily to make up for the afternoon trough. As explained, the afternoon trough between twice-daily and three times daily brimonidine dosing is about 3.25 mmHg. The data in Larsson showed that timolol only provided an additional 1.7 mmHg of IOP-lowering when it was added to brimonidine as adjunctive therapy. (DTX-1121 at Table 2; Trial Tr., Day 2 AM at 59:8–60:2 (Tanna).) The Clineschmidt paper further showed that the addition of timolol only added a maximum of 2.4 mmHg when added twice daily to dorzolamide in a fixed combination (DTX-1169 at Table 3; Trial Tr., Day 2

PM at 168:15–23 (Noecker)) and that 2.4 mmHg was at the morning time points, at which the timolol would be at its most effective, instead of the afternoon, when it would be expected to have less effect. (Trial Tr., Day 2 PM at 166:20-167:1, 168:24-169:2 (Noecker).)

152. Thus, the evidence presented at trial suggests that timolol added to twice-daily brimonidine as adjunctive therapy would not inherently be as effective as brimonidine dosed three times daily.

153. Allergan also presented evidence as to why the data in Konstas does not show inherency. Allergan's expert, Dr. Noecker, explained that a person of skill in the art would question the reliability of the Konstas data because the methodology used in the study is unorthodox and the results are inconsistent with other reported data. (*See* Trial Tr., Day 2 PM at 135:7-136:25 (Noecker); Trial Tr., Day 3 AM at 68:2–69:17 (Noecker).) In particular, Konstas measured IOP over a 24-hour period, which required taking IOP measurements on patients in the middle of the night. The IOP-lowering curve shown in Konstas suggests that IOP is at its lowest point overnight and at its highest in the mid-morning. (DTX-1397 at AGN_COMBI0438129.) Dr. Noecker explained that essentially all other data in the literature shows that IOP is generally higher, not lower, overnight. (Trial Tr., Day 2 PM at 136:3–21 (Noecker) ("There tends to be a drift up in eye pressure during the night in all other studies we've seen, and even on treatment or off treatment, even with our best drug, the prostaglandin analogues, and I would say that this data is inconsistent with any other study in the literature.").) Due to this inconsistency with other reported studies, a person of skill in the art would not simply accept the data in Konstas, without other evidence, as showing that the Combigan® fixed combination formulation has equivalent efficacy over a 24-hour period as the adjunctive twice-daily therapy. (Trial Tr., Day 3 AM at

69:6–17 (Noecker) ("[A] lot of the data does not agree with what we have seen, so it makes me question all of it, exactly how they got to that point.").)

154. The Court credits Dr. Noecker's testimony about the flaws in the Konstas paper. Moreover, Konstas did not measure adverse events, so it provides no additional comparison of the adverse event rates between Combigan® and adjunctive twice-daily therapy. Hence, it cannot support Defendants' inherency arguments related to the adverse event claims. Accordingly, the Court finds that Konstas does not show that either the claimed efficacy or safety limitations were inherent in prior art adjunctive therapy.

155. The Goni paper reports on the 507T clinical study (DTX-1102), which was a 3-month study run in Europe evaluating the use of the Combigan® formulation twice daily compared to the adjunctive use of 0.2% brimonidine and 0.5% timolol both twice daily in separate bottles. (DTX-1209 at AGN_COMBI0439583.) Goni concluded that the "[b]rimonidine/timolol fixed combination was as effective as concomitant therapy with respect to mean IOP and mean change from baseline IOP at all time points and visits." (*Id.* at AGN_COMBI0439581.) Goni also concluded that both the fixed combination and the twice-daily adjunctive treatments were well-tolerated and that there were no differences in adverse events between groups. (*Id.*) However, these conclusions in Goni do not demonstrate that the efficacy and side effect results of Combigan® are inherent in twice-daily adjunctive therapy.

156. In terms of efficacy, Goni's conclusion of equivalent efficacy of the fixed combination and twice-daily adjunctive therapy is based on data taken at only two time points—8:00 a.m. and 10:00 a.m. (Trial Tr., Day 2 PM at 171:8-172:4 (Noecker).) The study did not collect IOP measurements in the afternoon. As a result, there is no way to know whether the twice-daily adjunctive therapy was as effective as the Combigan® fixed combination

formulation at the critical afternoon trough point in time at which Combigan®'s efficacy is the most surprising. (*Id.*) Goni therefore does not demonstrate that the prior art twice-daily adjunctive therapy was inherently as effective as Combigan®.

157. As to side effects, Goni's conclusion that there is no difference in the side effect profile between the Combigan® fixed combination formulation and the twice-daily adjunctive therapy also does not show inherency. First, the 507T study reported on in Goni was run in patients who were already on a monotherapy regimen and therefore already tolerating that treatment. (Trial Tr., Day 1 AM at 123:25–124:8 (Batoosingh).) Ms. Batoosingh explained that this would likely account for lower rates of side effects:

> Q: You testified in cross-examination that the patients in the 507T study were largely already on therapy. Does that matter when looking at side effects?
> A: Yes.
> Q: Why?
> A: Because the patients who are on the therapies that are being tested are already used to the types of side effects—or even in the class of medication are used to those types of side effects. And so a change from baseline, which is what's reported in the clinical trials, is not necessarily demonstrative because it – it's influenced by what they're on at baseline.

(Trial Tr., Day 1 PM at 6:8–19 (Batoosingh).) Thus, because the patients in the 507T study were already on therapy and likely already tolerating those drugs, the side effects reported would be lower than they would be in a study that included patients being exposed to the drugs for the first time. (Trial Tr., Day 3 AM at 71:2–72:5 (Noecker) (explaining that the study design of Goni "will reduce the rate of adverse events because you're having people who are known to be successful already").)

158. Second, the 507T study reported on in Goni was only a 12-week study. The evidence at trial demonstrated that certain side effects, including allergic conjunctivitis in particular, can take longer than 12 weeks to develop in some patients. (Trial Tr., Day 1 AM at

106:11–107:6 (Batsoosingh.)) Therefore, 12 weeks of data may well not be sufficient to show the true allergy rate or the true difference in allergy rate between the two treatment groups.

159. Finally, the 507T study reported on in Goni took place in Europe and the Middle East, where side effect reporting is done differently than it is in many of the studies run in the United States. (DTX-1102.) Rather than asking about specific adverse events using a form with boxes to check for each one, adverse events data in Goni was collected by more generally asking patients how they were feeling. (DTX-1102; Trial Tr., Day 2 PM at 172:21–173:15 (Noecker).) Since the side effect data was collected differently, it is again likely that the reported rates would be lower than in many other studies, and an accurate comparison difficult if not impossible. (*Id.*) As Dr. Noecker analogized, the side effect reporting in the 507T was more of a "write-in" option, and "if it is an election, the write-in candidate is not going to show up very often." (Trial Tr., Day 2 PM at 172:21–173:8 (Noecker).) Not surprisingly, the rates reported in Goni for overall side effects of Combigan® are lower than those reported for the same treatment arm in other clinical studies. (*Compare* DTX-1209 at AGN_COMBI0439586 (reporting overall adverse event rate of 20.2% for patients on Combigan® in Goni study) *with* PTX-070-0007 (reporting overall adverse event rate of 53.0% in patients on Combigan® in Sherwood study).)

160. There is no way to know if the adverse event data reported in Goni would have been the same in a study of longer duration, that included patients who were not already tolerant to the drugs in the study, or that specifically inquired about particular adverse events in a more precise way. Goni therefore does not show that the reduction in adverse events as compared to brimonidine monotherapy three times daily seen with Combigan® is inherent in adjunctive twice-daily therapy.

161. The Court also notes that the asserted claims of the ’149 and ’425 patents compare the efficacy of a 0.2% brimonidine/0.5% timolol fixed combination dosed twice daily with 0.2% brimonidine monotherapy dosed three times daily. Defendants have presented no evidence as to how twice-daily adjunctive therapy with 0.2% brimonidine and 0.5% timolol would perform compared to 0.2% brimonidine dosed three times daily. Neither Goni nor Konstas address that comparison. (*See* Trial Tr., Day 3 AM at 66:5–17 (Noecker) (“Q: Was there any data in the prior art that showed that adjunctive therapy with brimonidine and timolol, each given twice per day, was as effective as three-times-a-day brimonidine monotherapy? A: No.”).) Consequently, there is no evidence that it would have the same performance as Combigan® when compared, as the claims require, to 0.2% brimonidine alone dosed three times a day.

5. Secondary Considerations of Non-Obviousness

162. The Court finds that secondary considerations, including unexpected results, long felt need, commercial success and copying, favor the conclusion that the claims of the patents-in-suit were not obvious.

a. Unexpected Results

163. Allergan’s clinical studies of Combigan® demonstrated unexpected results related both to efficacy and side effects of Combigan®, which are embodied in the asserted claims of the patents-in-suit.

164. As set forth above, the clinical trials for Combigan® demonstrated that Combigan® dosed twice daily shows statistically better or equivalent IOP lowering compared to 0.2% brimonidine monotherapy dosed three times daily. As inventor Ms. Batoosingh testified, this result was surprising and unexpected, particularly given that 0.2% brimonidine was required to be dosed three times per day in order to avoid the decrease in efficacy, or “afternoon trough.”

Neither the inventors nor practitioners in the field expected that Combigan® could fill in the afternoon trough, and maintain IOP-lowering efficacy throughout the day. The Court finds this unexpected result to be objective evidence supporting the non-obviousness of the asserted claims. This evidence supports the non-obviousness of claim 4 of the '149 patent, which claims Combigan®'s greater or equal efficacy compared to 0.2% brimonidine monotherapy, and claim 1 of the '976 patent, which claims a therapeutically effective composition.

165. The clinical trials for Combigan® also demonstrated an unexpected reduction in certain adverse events in patients receiving Combigan® compared to those receiving 0.2% brimonidine three times daily. As Ms. Batoosingh testified, although Allergan believed Combigan® could have, in general, an improved overall safety profile, none of the inventors believed that Combigan® would achieve the reductions in specific adverse events that were observed. (Trial Tr., Day 1 AM at 79:10–82:13 (Batoosingh.)) In particular, Combigan® exhibited a surprisingly lower incidence of allergic conjunctivitis, a problematic side effect associated with brimonidine, when compared to 0.2% brimonidine monotherapy. The reduction in allergic conjunctivitis was not simply due to the reduction in the numbers of doses of brimonidine, but rather is attributable to a synergistic effect of combining brimonidine and timolol in a single fixed-combination formulation. (Trial Tr., Day 1 AM at 79:10–83:13.) In addition to a lower incidence of ocular adverse events, Combigan® also unexpectedly demonstrated a reduction in nervous system side effects, such as somnolence and oral dryness. These reductions in adverse events were unexpected and are objective evidence supporting the non-obviousness of the asserted claims. This evidence supports the non-obviousness of claims 1–8 of the '425 patent, which explicitly recite the reduction of adverse events observed with

Combigan® compared to those observed with 0.2% brimonidine administered three times per day.

b. Closest Prior Art

166. Sandoz argued that all unexpected results must be evaluated against the closest prior art, which, according to Sandoz, is the adjunctive use of brimonidine and timolol twice daily. The Court has already found that the prior art on the twice-daily adjunctive use of the two compounds does not teach efficacy results, particularly at the afternoon trough time point, and does not teach rates of adverse events. In fact, based on the prior art, a person of skill in the art would have expected that twice daily brimonidine combined with timolol would not perform without loss of efficacy as compared to brimonidine alone three times daily because timolol would not have been expected to eliminate the afternoon trough for IOP lowering. Additionally, based on the prior art, including the known overlapping side effects of brimonidine and timolol and the experience with Cosopt®, a person of skill in the art would not have expected that combining brimonidine and timolol for twice-daily dosing would reduce adverse events as compared to brimonidine dosed three times a day.

167. Sandoz's entire argument as to what would have been "expected" based on the prior art twice-daily adjunctive therapy depends on information, including clinical studies of Combigan® itself, that is not actually in the prior art and would not have been available to inform the expectations of a person of skill in the art. Accordingly, the Court finds that the efficacy and side effect results of Combigan® are unexpected compared to all the prior art, including twice-daily adjunctive therapy, based properly on what was knowable through such prior art.

c. Long-Felt Need

168. As of 2002, there was a long-felt need for a fixed combination product to treat glaucoma. (Trial Tr., Day 2 PM at 182:18–183:4 (Noecker).) The inventions disclosed and claimed in the patents-in-suit provided a long-awaited fixed combination that lowered IOP as well or better than existing adjunctive solutions, such as 0.2% brimonidine, and that also reduced some of the problematic adverse events associated with brimonidine. (Trial Tr., Day 2 PM at 182:18–183:4 (Noecker).)

d. Copying

169. It is undisputed that Sandoz's proposed product is an exact copy of Combigan®. (Trial Tr., Day 2 PM at 182:3–8 (Noecker); *see also* Trial Tr., Day 1 PM at 38:23–25 (Noecker); Day 2 AM at 39:8-11 (Tanna).) Sandoz sold both a generic 0.2% brimonidine product and a generic 0.5% timolol product before Allergan filed the patents-in-suit. (Trial Tr., Day 2 PM at 182:9–17 (Noecker).) There was nothing to stop Sandoz from developing its own fixed combination product of brimonidine and timolol, but it did not do so. Instead, Sandoz copied Combigan®. Therefore, the Court finds that the interest of Sandoz in copying the claimed inventions provides further support for a finding that the asserted claims are not obvious.

e. Commercial Success

170. The commercial success of Combigan® also demonstrates that the asserted claims of the '149, '976, and '425 patents are not obvious. Since it launched in 2007, gross sales of Combigan® have increased year after year. (Trial Tr., Day 2 PM at 66:12–18 (LeCause); PTX-356.) Net sales of Combigan® in 2015 were approximately $350 million, and are expected to be roughly $370 million in 2016. (Trial Tr., Day 2 PM at 66:12–67:5 (LeCause).) Moreover, Combigan® has been a profitable product for Allergan, and is one of the most significant

contributors to the profitability of Allergan's U.S. eye care business. (Trial Tr., Day 2 PM at 70:16-71:10, 72:14-73:3 (LeCause); 104:16–105:22 (Maness).)

171. The success of Combigan® is substantially related to the features recited in the asserted claims. Economic evidence demonstrates that the success of Combigan® is not due only to the success of its two active ingredients, brimonidine and timolol. Brimonidine and timolol were available in a generic form for a lower combined cost than Combigan®, yet Combigan® still achieved substantial sales. (Trial Tr., Day 2 PM at 106:2–107:17 (Maness).) Rather, advertising and marketing information show that a significant contributor to the success of Combigan®, in addition to its IOP-lowering efficacy, was the lower incidence of side effects observed compared to brimonidine monotherapy, in particular the reduction in ocular allergy. (Trial Tr., Day 2 PM at 108:23–112:14 (Maness).) Based on this advertising and marketing evidence, the Court finds that the IOP-lowering efficacy and reduction in side effects of Combigan®, both central components of the patents-in-suit, are substantially related to Combigan®'s commercial success.

6. Enablement and Written Description

172. The Court has previously held that Sandoz is not precluded from challenging the validity of claim 4 of the '149 patent for lack of enablement and written description. (Dkt. No. 314.) Allergan maintains its arguments as to preclusion of those defenses.

173. At trial, Sandoz argued that claim 4 of the '149 patent and claim 1 of the '976 patent are invalid for lack of enablement and lack of written description under 35 U.S.C. § 112. Defendants did not address its enablement or written description defense for the claims of the '425 patent.

a. The Claims Cover Six Possible Combinations of Brimonidine and Timolol

174. The evidence at trial demonstrated that a person of skill in the art would understand there to be six possible combinations of brimonidine and timolol encompassed by the claims: (1) 0.2% brimonidine tartrate/0.5% timolol free base; (2) 0.2% brimonidine tartrate/0.5% timolol maleate; (3) 0.2% brimonidine tartrate/0.5% timolol tartrate; (4) 0.2% brimonidine free base/0.5% timolol free base; (5) 0.2% brimonidine free base/0.5% timolol maleate; and (6) 0.2% brimonidine free base/0.5% timolol tartrate.

175. Brimonidine tartrate was the only salt of brimonidine known and used as of the 2002 filing date of the patents. (Trial Tr., Day 2 PM at 188:1–17 (Noecker).) A person of skill in the art would have known that the free base form also exists in solution. (*Id.* at 188:18–23.) For timolol, timolol maleate was the only salt form known and used in the art in 2002, and a person of skill in the art would also have been aware that the timolol base form exists in solution. (*Id.* at 188:24–189:3.)

176. Moreover, as the Court explained in its Markman order in Combigan® II, timolol tartrate is also described in the file history of the patents-in-suit. (*Allergan II*, Dkt. 171 at 15–16.) Therefore, a person of skill in the art would understand that it is encompassed by the claims based on the file history. (*Id.*; Trial Tr., Day 2 PM at 189:4-20 (Noecker).)

b. Sandoz's Argument that the Claims Cover Hundreds of Possible Combinations Is Not Supported by the Evidence

177. Sandoz presented no testimony from their experts to support its arguments that the claims cover potentially hundreds of salts of brimonidine and timolol.

178. Dr. Tanna testified in conclusory fashion that "based on the Court's claim construction regarding the brimonidine and timolol terms, the composition can be many, many different things because there are many different salts of brimonidine and many salts of timolol

and their respective free bases as well." (Trial Tr., Day 1 PM at 167:10–168:6 (Tanna).) Dr. Tanna did not identify a single additional salt other than brimonidine tartrate and timolol maleate. This was noted by Dr. Noecker. Dr. Tanna also cited no reference to support his suggestion that the "there is a huge broad family, probably hundreds of different things, that could fit within the scope of this claim." (*Id.*) This conclusory and unsupported testimony is not credible and is inconsistent with the evidence about what a person of skill in the art would understand about the application of the terms.

179. Sandoz attempted to support its arguments through exhibits introduced during cross-examination of Allergan's expert, Dr. Noecker. Without any expert testimony to explain those documents, the Court is not persuaded by Sandoz's arguments. U.S. Patent Nos. 3,890,319 (the "'319 patent") and 3,655,663 (the "'663 patent") (DTX-1358 and DTX-1365) that Defendants rely on are directed to broad classes of compounds, not just to brimonidine and timolol. Contrary to Sandoz's arguments, these patents do not establish that persons of skill in the art would understand that there are numerous salts of brimonidine and timolol.

180. The '319 patent lists a number of potential salts for the quinoxaline compounds described therein, but it does not say that any of the listed salts could be made with brimonidine specifically, that any of the salts would be acceptable for ophthalmic use, or that any of the salts had actually been made with any compound at all. (Trial Tr., Day 3 AM at 62:20–63:16 (Noecker).) The Court notes that the salt example Sandoz relies on in the '319 patent is a prophetic example, and not a list of salts actually made. (DTX-1358 at 10:37–58.)

181. There was no dispute at trial that the only salt of brimonidine available in the real world as of 2002 was brimonidine tartrate. (Trial Tr., Day 3 AM at 63:17–21.)

182. The ’663 patent also lists a number of potential salts but does not say whether any of those salts could actually be made with any particular compound or whether any of them would be acceptable for ophthalmic use if they were made with any of those particular compounds. (Trial Tr., Day 3 AM at 63:22–65:13 (Noecker).)

183. There was no dispute at trial that there is only one salt of timolol actually available in the art—timolol maleate. (*Id.* at 65:4–8.) Indeed, the maleate salt is the only salt that the ’663 patent actually discloses as an example for the specific compound of timolol, providing further support for Allergan’s position, and counter to Sandoz’s position. (*Id.* at 63:22–64:9; DTX–1365 at Example 1A.) Again, the recitation of other salts in the ’663 patent is prophetic.

184. The hypothetical salts of brimonidine and timolol proposed by Sandoz were not supported by any expert testimony, and the Court rejects Defendants’ argument to read the claim construction as “not limited to real world salt forms.” (Trial Tr., Day 3 AM at 115:2–5.)

c. The Specification Discloses a Fixed Combination Formulation and a Clinical Study Showing that it Achieved the Claimed Results

185. The specification of the patents-in-suit discloses both the specific formulation of Combigan® as well as both the protocol for and results of a clinical study that was run on that formulation. (Trial Tr., Day 2 PM at 185:5–187:25 (Noecker).) The protocol provides details to inform a person of skill in the art how the trial was run and how a similar trial could be conducted, including details about patient enrollment, what drugs and groups to use, how to dose the drugs, and how to measure the effectiveness and side effects. (*Id.* at 185:24–186:18.) The reported results for the brimonidine/timolol fixed combination formulation dosed twice daily demonstrated that “[i]n terms of reducing intraocular pressure, it performed as well or better than brimonidine dosed three times a day, and in terms of rates of adverse events, it had a more

favorable profile." (*Id.* at 187:12–25 (Noecker).) Those results are recited in the asserted claims, with claim 4 of the '149 patent requiring no loss of efficacy with twice-daily dosing of the fixed combination as compared to brimonidine alone three times a day and claim 1 of the '976 patent requiring that twice-daily dosing of the fixed combination be therapeutically effective.

186. A person of skill in the art reading the specification would therefore be able to prepare a fixed combination formulation of 0.2% brimonidine and 0.5% timolol that would meet the clinical limitations of the asserted claims.

187. While, the specification contains only one example of a formulation of 0.2% brimonidine tartrate and 0.5% timolol base (equivalent to 0.68% timolol maleate), the single example is representative of the full scope of the claim. The presence of only one example does not render the claims invalid for lack of enablement and written description.

188. Allergan demonstrated at trial that a person of skill in the art would have no problem converting between the several forms of brimonidine and timolol that are covered by the claims as a matter of basic math, using the molecular weights of the compounds to calculate the ratios. (Trial Tr., Day 2 PM at 189:21–190:25 (Noecker).) For example, 0.2% brimonidine tartrate is equal to 0.132% brimonidine free base, and 0.5% timolol free base is equal to 0.68% timolol maleate and to 0.73% timolol tartrate. (PDX-332.) This testimony was unrebutted by Sandoz.

189. The evidence at trial also showed that brimonidine is effective at lowering IOP at concentrations of 0.08% to 0.5%, while timolol has approximately equal efficacy at concentrations of 0.25% and 0.5%. (Trial Tr., Day 2 PM at 191:1-20 (Noecker).) As Dr. Noecker explained, the concentrations that a person of skill in the art could calculate from the six

different forms of brimonidine and timolol covered by the claims all fall well within that effective range. (*Id.*) This testimony was unrebutted.

190. Dr. Noecker also testified that the example in the patent would be representative of the other forms of brimonidine and timolol covered by the claims. (*Id.* at 192:1-20.) A person of skill in the art would expect that the brimonidine and timolol forms covered by the claims would perform in the same way as the disclosed example. Sandoz presented no evidence to counter that testimony or to show that a person skilled in the art would not expect the example to be representative.

191. Sandoz's only expert to testify as to enablement and written description, Dr. Tanna, merely relied on his incorrect assertion that the claims encompassed hundreds of possible combinations and, even there, did not explain why the example would not be reasonably representative. The Court rejects Dr. Tanna's testimony and credits the testimony from Dr. Noecker that the clinical example in the patent is representative of the full scope of claim 4 of the '149 patent and claim 1 of the '976 patent.

d. The Specification Informs a Person of Skill in the Art How to Run a Clinical Trial

192. The patents-in-suit provide instructions on how to run a clinical trial to confirm that the efficacy and side effect profile for a particular fixed combination formulation of 0.2% brimonidine and 0.5% timolol.

193. Example 2 of the patents-in-suit lays out the clinical protocol in detail, instructing a person of skill in the art precisely how to run a trial to test the efficacy and side effect profile of a fixed combination formulation dosed twice daily as compared to brimonidine dosed three times a day. (Trial Tr., Day 2 PM at 192:11–20 (Noecker).)

194. Dr. Noecker explained that, in light of the disclosures in the specification, running such a trial would not constitute undue experimentation. (*Id.* at 192:18–20.)

195. As Ms. Batoosingh testified, the cost of a clinical trial at the relevant time was about $2,500 per completed subject, which is not a prohibitive expenditure. (Trial Tr., Day 1 AM at 66:25–67:8 (Batoosingh).)

CONCLUSIONS OF LAW

I. INFRINGEMENT

A. Legal Standard

1. Infringement Under 35 U.S.C. § 271(e)(2)(A)

1. The Hatch-Waxman Act provides that it shall be an act of infringement to submit an ANDA application "for a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2)(A). "Under § 271(e)(2)(A) a court must determine whether, if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569-70 (Fed. Cir. 1997).

2. Infringement is a question of fact, *e.g.*, *Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V.*, 528 F.3d 1365, 1382 (Fed. Cir. 2008), and must be proven by a preponderance of the evidence, *e.g.*, *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1310 (Fed. Cir. 2005). The same preponderance of the evidence burden applies to patentees asserting infringement under 35 U.S.C. § 271(e)(2). *Dey, L.P. v. Teva Parenteral Medicines, Inc.*, 958 F. Supp. 2d 654, 660 (N.D.W. Va. 2013).

3. Determining literal infringement requires (1) construing the claims and (2) determining whether the properly construed claims read on the accused product or method.

ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc., 694 F.3d 1312, 1319 (Fed. Cir. 2012) (quoting *Georgia–Pacific Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1330 (Fed. Cir. 1999)).

4. For purposes of infringement under 35 U.S.C. § 271(e)(2)(A), Sandoz's ANDA controls the infringement inquiry. "Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Abbott Labs v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). In other words, what an ANDA applicant "has asked the FDA to approve as a regulatory matter is the subject matter that determines whether infringement will occur." *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1278 (Fed. Cir. 2013).

2. Infringement Under 35 U.S.C. § 271(b)

5. Even if a defendant does not directly infringe a claim, the defendant may infringe the claim indirectly by playing a role in another's direct infringement of the claim. There are two types of indirect infringement: (1) inducement, and (2) contributory infringement. *In re Bill of Lading Transmission & Processing Sys. Patent Litig.*, 681 F.3d 1323, 1333 (Fed. Cir. 2012).

6. A defendant induces infringement if it (a) knows of the patents-in-suit, (b) encourages others (like patients, pharmacists, and doctors) to infringe and intends for them to do so, and (c) others (like patients, pharmacists, and doctors) will actually use the products in the infringing manner if they are approved. 35 U.S.C. § 271(b); *Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010).

7. The Federal Circuit has held that if a proposed drug's package insert instructs users to perform a patented method, then the package insert provides evidence of an affirmative intent to induce infringement of the patented method. *Astrazeneca, LP v. Apotex, Inc.*, 633 F.3d 1042, 1058-61 (Fed. Cir. 2010). The Federal Circuit has "long held that the sale of a product

specifically labeled for use in a patented method constitutes inducement to infringe that patent." *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 Fed. Appx. 917, 926 (Fed. Cir. 2011). A specific intent to induce infringement is present where the proposed package insert "would inevitably lead some consumers to practice the claimed method." *AstraZeneca*, 633 F.3d at 1060.

8. A generic product package insert does not need to specify each and every claim limitation to induce infringement. *See Hoffman LaRoche v. Apotex*, Nos. 07-4417 et al., 2010 WL 3522786, at *3 n.2 (D.N.J. Sept. 2, 2010) ("There is no requirement that the language used to induce infringement mirror the language of the claim."); *see also AstraZeneca*, 633 F.3d at 1057 (affirming district court's induced infringement determination based on labeling language that "implicitly instructed users" to practice patented methods).

3. Infringement Under 35 U.S.C. § 271(c)

9. A defendant is liable for contributory infringement if (a) it knows of the patents-in-suit, (b) it will sell products that others use to directly infringe the patent, (c) defendant's product is a material part of the invention, and (d) the product has no substantial non-infringing uses and is not a staple article of commerce. 35 U.S.C. § 271(c); *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 850-51 (Fed. Cir. 2010), *aff'd* 564 U.S. 91 (2011). *See also Eli Lilly*, 435 Fed. Appx. At 927 (holding generic defendants liable for contributory infringement where the FDA-authorized use was patented because "defendants are restricted from selling a federally regulated drug for unapproved uses").

B. Sandoz's Proposed Product Does Not Infringe the Claims of the '149 and '976 Patents Because It Does Not Meet the Concentration Limitation of the Claims

10. For the reasons stated above in paragraphs 81–88[3], Sandoz's proposed product will not meet each and every limitation of the asserted claims. In particular, the Court finds that Combigan® contains, and Sandoz's proposed product will contain 0.2% brimonidine tartrate, which reduces to 0.132% w/v brimonidine, and 0.68% timolol maleate, which reduces to 0.5% w/v timolol. This does not meet the fixed combination of 0.2% w/v brimonidine and 0.5% timolol claimed in the '149 and '976 patents.

11. Accordingly, Sandoz does not infringe the '149 and '976 patents, directly or indirectly.

C. Sandoz Is Liable for Infringement of the '425 Patent Under 35 U.S.C. §§ 271(b), (c), (e)(2)(A)

12. For the reasons stated above in paragraphs 81–96, use of Sandoz's proposed product will meet all the limitations of the asserted claims of the '425 patent. In particular, the Court finds that both Combigan® and Sandoz's proposed product contains 0.2% w/v brimonidine tartrate and 0.5% timolol free base as required by the claims of the '425 patents.

13. Sandoz does not contest any other limitation of the asserted claims of the '425 patent. Accordingly, for the reasons stated above in paragraphs 88–96, all other claim limitations of the asserted claims of the '425 patent are met by the use of Sandoz's proposed product. Therefore, Sandoz's proposed product infringes the '425 patent under 35 U.S.C. § 271(e)(2)(A).

14. Additionally, for the reasons stated above in paragraphs 97–104, Sandoz would induce and contribute to infringement of the '425 patent.

[3] Unless otherwise specified, the Court's reference to prior paragraphs here and throughout its Conclusions of Law refers to paragraphs contained in the Court's Findings of Facts.

II. INVALIDITY

A. Burden of Proof

15. Patents are presumed valid, and the accused infringer has the burden to prove invalidity by clear and convincing evidence. 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd. P'ship.*, 564 U.S. 91, 95 (2011).

16. Where, as here, nearly all of the art that is cited by the defendant was before the PTO during prosecution of the asserted patents, the defendant faces an "enhanced burden." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011) ("[A]lthough the standard of proof does not depart from that of clear and convincing evidence, a party challenging validity shoulders an enhanced burden if the invalidity argument relies on the same prior art considered during examination by the U.S. Patent and Trademark Office.").

B. Sandoz Put Forth No Evidence that the Asserted Claims of the Patents-In-Suit Are Invalid as Anticipated

17. Despite the fact that Sandoz's pleadings included affirmative defenses and counterclaims of invalidity of the '140, '976, and '425 patents as anticipated under § 102, it failed to put forth any evidence at trial of a single prior art reference which anticipated any of the patents-in-suit. Accordingly, the Court granted Allergan's motion under Rule 52(c) of the Federal Rules of Civil Procedure for judgment as a matter of law that the patents-in-suit were not invalid as anticipated under § 102.

C. Obviousness

1. Legal Standards

a. Generally

18. The ultimate issue of obviousness is an issue of law, but it is based on underlying factual findings, including "(1) the scope and content of the prior art; (2) the differences between

the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness." *In re Cyclobenzaprine*, 676 F.3d 1063, 1068 (Fed. Cir. 2012). Further, "a party seeking to invalidate a patent as obvious must demonstrate by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *Id.* at 1068–69 (quotations omitted).

19. Obviousness is analyzed from the perspective of one of skill in the art at the time of the invention and the use of hindsight is not permitted. *See KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) (recognizing "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness); *see also Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36 (1966) (discussing the "importance of guard[ing] against slipping into the use of hindsight … and resist[ing] the temptation to read into the prior art the teachings of the invention in issue" when considering the obviousness of a patent). "Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." *In re NTP*, 654 F.3d 1279, 1299 (Fed. Cir. 2011).

20. In an unpredictable art, like ophthalmic formulation development and treatment of patients, results are more likely to be unexpected and, thus, nonobvious. *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.").

b. Inherency

21. The Federal Circuit has explained that "the use of inherency, a doctrine originally rooted in anticipation, must be carefully circumscribed in the context of obviousness." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (concluding that the District Court erred in its inherency analysis). "[T]he concept of inherency must be limited when applied to obviousness," and a defendant must "meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Id.* at 1195–96 (Fed. Cir. 2014). That is, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1196 (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). However, if "the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient." *Id.*

c. Secondary Considerations

22. Objective indicia of non-obviousness, also referred to as secondary considerations, include copying, commercial success, failure of others, long-felt need, general skepticism of those in the art, and unexpected results. *See KSR*, 550 U.S. at 406. "Objective indicia may often be the most probative and cogent evidence of nonobviousness in the record." *Catalina Lighting, Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002). This is because the objective evidence can "often serve as insurance against the insidious attraction of the siren hindsight when confronted with a difficult task of evaluating the prior art." *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983). It is an important "check

against hindsight bias" because "knowing that the inventor succeeded in making the patented invention, a fact finder might develop a hunch that the claimed invention was obvious, and then construct a selective version of the facts that confirms the hunch. This is precisely why the Supreme Court explained that objective considerations might prevent a fact finder from falling into such a trap." *In re Cyclobenzaprine*, 676 F.3d at 1079. "Obviousness requires a court to walk a tightrope blindfolded (to avoid hindsight)—an enterprise best pursued with the safety net of objective evidence." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012).

23. The objective evidence of non-obviousness must be considered as part of the entire obviousness analysis, not merely after looking at all the evidence of obviousness that has been put forward. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc*., 688 F.3d 1342, 1360 (Fed. Cir. 2012); *In re Cyclobenzaprine*, 676 F.3d at 1075. Indeed, "[t]he objective considerations, when considered with the balance of the obviousness evidence in the record, guard as a check against hindsight bias." *Id*. at 1079.

24. "Unexpected results are useful to show the 'improved properties provided by the claimed compositions are much greater than would have been predicted.'" *Leo Pharm. Products, Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Results are unexpected when "the claimed invention exhibits some superior property or advantage that a person in the relevant art would have found surprising or unexpected" because "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750 (Fed.Cir.1995); *see also Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462 (Fed. Cir. 1984) (reversing obviousness finding where although the claimed invention combined two prior art devices, the district court overlooked "unexpected results nowhere suggested in the prior art").

2. The ’149 and ’976 Patents Are Not Invalid as Obvious

25. While the fixed combination of brimonidine and timolol may be obvious, for the reasons stated in paragraphs 105–171, the combination coupled with the twice a day application is not obvious. In particular, as the Federal Circuit previously held in *Allergan I*, Sandoz has not identified clear and convincing evidence in the prior art that the addition of timolol to brimonidine dosed twice per day would eliminate the afternoon trough.

26. Further, the Court concludes and holds that Sandoz did not demonstrate by clear and convincing evidence that the ’149 and ’976 patents were invalid as obvious under the doctrine of inherency. In particular, the Court concludes that the “no loss of efficacy” limitation is not inherent in all fixed combination formulations of the claimed brimonidine and timolol combinations. For the reasons stated in paragraphs 146–161, Sandoz has not shown by clear and convincing evidence that every fixed combination of brimonidine and timolol satisfies the “no loss of efficacy” limitation.

27. Additionally, for the reasons stated in paragraphs 162–171, the Court concludes and holds that secondary considerations of non-obviousness support this Court’s finding that the ’149 and ’976 patents are not invalid as obvious.

3. The ’425 Patent Is Not Invalid as Obvious

28. For the reasons stated in paragraphs 105–171, the Court concludes and holds that the ’425 patent is not invalid as obvious. In particular, and as discussed in relation to the ’149 and ’976 patents, Sandoz failed to prove by clear and convincing evidence that the combination and application elements of the ’425 patent would be obvious in light of the prior art. Additionally, Sandoz has failed to prove by clear and convincing evidence that the ’425 patent’s limitations regarding the reduction of adverse events would have been obvious in light of the prior art.

29. Further, the Court concludes and holds that Sandoz is unable to demonstrate by clear and convincing evidence that the ’425 patent was invalid as obvious under the doctrine of inherency. In particular, the Court concludes that the reduction in adverse events is not inherent in all fixed combination formulations of the claimed brimonidine and timolol combinations. Additionally, for the ’425 patent to be invalid under the doctrine of inherency in the context of an obviousness challenge, the reduction in adverse events would have to be the necessary result of claimed limitations which are themselves obvious. Therefore, the reduction in adverse events would have to be the necessary result of the combination of brimonidine and timolol *alone*, the only portion of the patents-in-suit which is obvious. If the reduction in adverse events results from the combination of brimonidine and timolol *plus* the specific application of the combination claimed in the patents-in-suit, then the ’425 patent is not invalid as obvious due to inherency. This is to say, that it is not enough that the reduction in side effects is inherent to the combination *and* application. Rather, the reduction in adverse events must be inherent from the combination alone, *i.e.*, a necessary consequence of using the combination. For the reasons stated in paragraphs 146–161, Sandoz has not shown by clear and convincing evidence that the combination alone necessarily results in reduction of side effects.

30. Additionally, for the reasons stated in paragraphs 162–171, the Court concludes and holds that secondary considerations of non-obviousness support the conclusion that the ’425 patent is not invalid as obvious.

D. Written Description and Lack of Enablement

1. Legal Standards

a. Written Description

31. Written description of a genus requires the disclosure of either a representative number of species falling within the scope of the genus, or structural features common to the

members of the genus so that one of skill in the art can "visualize or recognize" the members of the genus. *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 730 (Fed. Cir. 2014). A single representative embodiment can support an adequate written description of a claimed genus. *See, e.g., Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 1073 (Fed. Cir. 2005) (finding sufficient written description where the specification disclosed a representative embodiment of the claimed genus); *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed. Cir. 2004) (referring to "general rule" that disclosure of a species provides sufficient written description support for a genus claim); *see also Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1352 (Fed. Cir. 2011) ("There is no special rule for supporting a genus by the disclosure of a species; so long as disclosure of the species is sufficient to convey to one skilled in the art that the inventor possessed the subject matter of the genus, the genus will be supported by an adequate written description.").

b. Enablement

32. A patent is enabling if its disclosure is sufficient to enable a person of ordinary skill in the art to make and use the claimed inventions without undue experimentation; it "need not teach, and preferably omits, what is well known in the art." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Warner-Lambert Co. v. Teva Pharms. USA*, 418 F.3d 1326, 1337 (Fed. Cir. 2005).

33. Some experimentation is permissible, so long as it is not "undue." *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988) (explaining that enablement is not negated by the necessity for some experimentation and setting forth factors to consider in determining whether such experimentation is undue). Importantly, in this analysis, a person of skill in the art is assumed to have the patent specification as a guide to teach them the claimed invention. *See AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (explaining that in determining

whether a patent claim is enabled, the question is whether using the patent specification as an initial guide, the hypothetical skilled artisan's knowledge of the surrounding art and ability to modestly experiment would have been sufficient to enable him to make and use the claimed invention); *see also Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004) (explaining that the specification itself need not necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art).

2. Claim 4 of the '149 Patent Is Not Invalid For Lack of Written Description

34. Defendants did not present any evidence or argument on a written description defense at trial as to the claims of the '425 and '976 patents.

35. As to claim 4 of the '149 patent, for the reasons stated above in paragraphs 172–191, under the Court's construction of the claims, such includes only six possible combinations of brimonidine and timolol that would be apparent to one of skill in the art. The specification provides a clinical example of one of those combinations—the particular combination that is used in the Combigan® formulation—and demonstrates that this formulation dosed twice daily has equivalent IOP-lowering efficacy and a lower incidence of adverse events as compared to 0.2% brimonidine tartrate monotherapy dosed three times daily. The example in the specification is therefore representative of, and provides a sufficient written description for, the small genus encompassed within the claims.

36. Moreover, for the reasons stated above in paragraphs 177–184, the Court finds that it would be improper to require written description support for hypothetical salts that Sandoz has not proven actually existed anywhere in the art. Language in a specification is to be

understood for what it meant to one having ordinary skill in the art at the time the application was filed. *See United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251–52 (Fed. Cir. 1989) (rejecting evidence directed to a later state of the art and explaining that to require patentees to disclose future developments in the science would "impose an impossible burden on inventors and thus on the patent system"); *see also, Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1331 (Fed. Cir. 2003) (agreeing with the district court's conclusion that "when the claim is to a composition rather than a process, the written description requirement does not demand that the specification describe technological developments in the way in which the claimed composition is made that may arise after the patent application is filed.").

37. Therefore, for the reasons stated above in paragraphs 172–191, the Court finds that Sandoz has failed, by clear and convincing evidence, to prove invalidity of claim 4 of the '149 patent for lack of written description.

3. Claim 4 of the '149 Patent Is Not Invalid For Lack of Enablement

38. For the reasons stated above in paragraphs 172–195, the Court finds that Sandoz failed to meet its burden to show by way of testimony or documentary evidence that any amount of experimentation, if needed, would be undue. *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013). The "mere potential need for clinical work" does not constitute undue experimentation. *Id.* at 1338-1339. *See also Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365–66 (Fed. Cir. 2008) ("[E]ven if clinical trials informed the anticonvulsively effective amount, this record does not show that extensive or 'undue' tests would be required to practice the invention.").

39. Sandoz did not present any evidence or argument at trial as to a lack of enablement defense relating to the claims of the '425 and '976 patents.

40. As to claim 4 of the ’149 patent, for the reasons stated above in paragraphs 174–184, under the Court’s construction of the claims, only six possible combinations of brimonidine and timolol would be apparent to one of skill in the art. The specification provides a clinical example of one of those combinations—the particular combination that is used in the Combigan® formulation—and it demonstrates that this formulation dosed twice daily has equivalent IOP-lowering efficacy and a lower incidence of adverse events as compared to 0.2% brimonidine tartrate monotherapy dosed three times daily. The example in the specification is representative of, and enables, the small genus encompassed within the claims.

41. Moreover, for the reasons stated above in paragraphs 174–184, the Court concludes and holds that it would be improper to require enablement for hypothetical salts that have not been proven to have actually existed in the art. *See United States Steel Corp.*, 865 F.2d at 1251–52 (rejecting evidence directed to a later state of the art and explaining that to require patentees to disclose future developments in the science would “impose an impossible burden on inventors and thus on the patent system”); *see also Amgen*, 314 F.3d at 1335 (a specification’s failure to disclose the “later-developed” technology cannot invalidate the patent for lack of enablement).

42. Therefore, the Court finds that Defendants have failed, by clear and convincing evidence, to prove invalidity of claim 4 of the ’149 patent for lack of enablement.

CONCLUSION

For the reasons set forth above, the Court finds, concludes and holds that: (1) Sandoz’s proposed product does not infringe the ’149 and ’976 patents; (2) Sandoz’s proposed product infringes the ’425 patent under 35 U.S.C. §§ 271(e)(2)(A) and 271(b); and (3) none of the patents-in-suit is invalid. Accordingly, the Court hereby **ORDERS** that the effective date for the

approval of Sandoz's ANDA to be the date no sooner than the latest expiration date of the patents-in-suit. Any conduct by Sandoz to market any product described within its ANDA prior to such effective approval date is hereby **ENJOINED**.

So ORDERED and SIGNED this 30th day of December, 2016.

RODNEY GILSTRAP
UNITED STATES DISTRICT JUDGE